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CERVICAL CANCER: A DISORDERED GROWTH RESPONSE TO INFLAMMATION IN THE PRESENCE OF ESTROGEN EXCESS AND NUTRITIONAL DEFICIENCY*

Cytological, Clinical, Nutritional, and Pathologic Studies

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EVIDENCE that a type of human cancer is associated with a metabolic disturbance characterized by a nutritional deficiency, an estrogen excess, and an inflammatory reaction is herein presented. The inference is that uterine cervical cancer may be the abnormal type of inflammatory response to chronic infection which occurs in the presence of a nutritional deficiency of thiamine† and an associated excess of the specific growth-hormone estrogen.

Squamous carcinoma of the cervix is perhaps the type of cancer best suited for research investigation in humans. This type of cancer arises from a known localized focus, the squamocolumnar circle, according to such eminent pathologists as Novak,[1] TeLinde and Galvin[2] and associates. From this single spot, cancer originates more commonly than from any other known area in the human body! This area is accessible to the examining eye and finger, it is readily accessible for biopsy, its functions in health and disease are fairly well understood, and its reactivity to hormonal function is limited by tissue selectivity. The recent advent of the discovery of cytology techniques as a means of providing further information regarding cervical cell changes in association with changing estrogen levels and cervical infection provides what we believe to be a most significant addition to the surgical biopsy. While biopsies are seldom taken with great frequency, cervical cell-smears may be taken daily, and the morphologic nuclear changes found in the constantly exfoliating squamous cells provide fascinating evidence of growth activity. When these microscopic nuclear phenomena are

*Aided by a grant from Ortho Research Foundation.

†Thiamine indicates "Thiomine and/or Riboflavin" throughout paper.

correlated with available clinical evidence, biochemical evidence and pathologic tissue studies, the interpretation of neoplastic growth propensities is greatly enhanced.

During the course of studying vaginal and cervical cytology smears for a diagnosis of uterine cancer, it was observed that a high percentage of our first two hundred cases proved to be cancer showed evidence of abnormally high endogenous estrogenic activity. This was first observed and reported by us in 1944.[3] The observation assumed more than passing significance when a patient 70 years of age suffering from cervical carcinoma manifested a cytology picture of estrogenic cornification similar to that of a young woman in the regenerative phase of the sex cycle. The nature of the associated growth factor was confirmed in the proliferative pattern of the endometrium. Since this time all of our cancers have been studied carefully for evidence of estrogenic cornification using a special cytology technique which will be described later. Over 75 per cent of the cases have shown evidence of abnormal cornification, regardless of age.

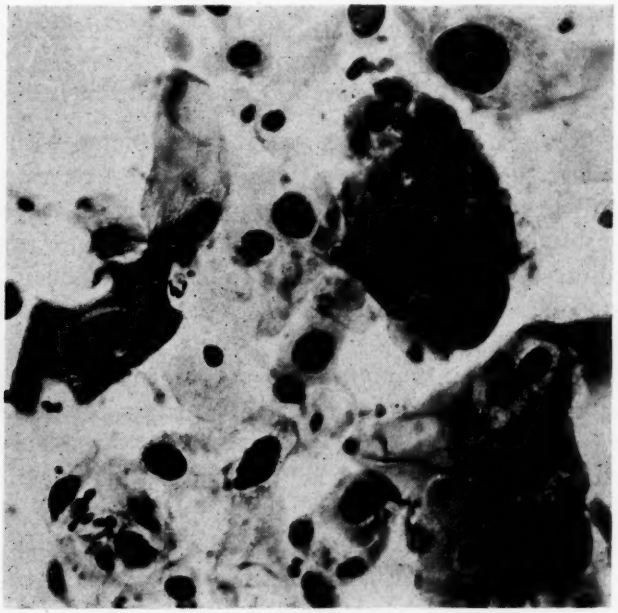

Fig. 1.—Cervical cytology smear in postmenopausal case of squamous carcinoma of cervix showing malignant cells and estrogenic cornified cells in close association. Note extreme nuclear variability in cancer cells.

Cytology studies have been made in over 3,500 cases, using a modification of the ingenious technique originated by Papanicolaou and Traut.[4] It has become apparent that this method of study puts at the disposal of the medical profession a simple means of not only providing early uterine cancer diagnosis, but also of estimating the endogenous tissue estrogens of the body which may be causally related to the disease.

More recently, and almost by accident, we discovered the presence of a nutritional deficiency of thiamine to be frequently present in cases manifesting

abnormal estrogenic cornification. The linkage of these two factors was first recognized by us in three cases which will be discussed in some detail. A preliminary report of our findings in these cases and in a small group of cases of known cancer and menorrhagia was recently made in *Science*.[5] It is proposed in this report to present our findings and further observations on a series of 100 patients investigated from a combined nutritional, cytologic, clinical, and pathologic approach. Fifty of these were proved cases of cervical cancer, fifty were normal controls. Photomicrographs of some of the cytologic and pathologic evidence will be presented, and the results will be tabulated.

Studies of Endogenous Estrogen

Perusal of the scientific literature reveals considerable experimental evidence in animals to support a nutritional-hormonal relationship acting through the liver. Recent studies of liver function in dietary deficiency would appear to indicate impairment of this organ in its ability to inactivate estrogen. One

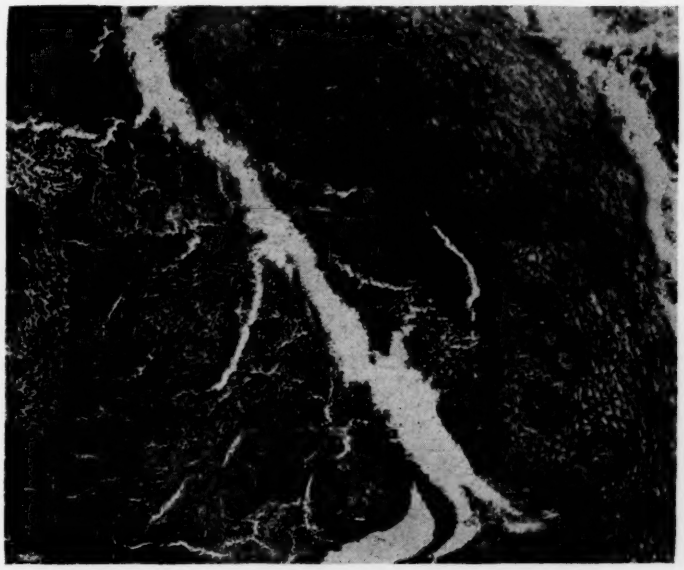

Fig. 2.—Biopsy of cervix. Note squamous epithelium adjacent to carcinomatous growth in patient 65 years of age. The cornified cells are evident on the surface. The depth of the squamous epithelium is indicative of active estrogenic growth stimulation. This picture is very much different from the thin atrophic epithelium found in normal postmenopausal cases.

wonders whether the human liver is similarly influenced in its function. If so, the urinary estrogens would vary appreciably with liver function as well as with ovarian production. While blood levels should give a true picture, most methods of determining this are complicated and unsatisfactory. There appear to be many unknowns in the metabolism of endogenous estrogen. Heard,[6] who has investigated steroid metabolism intensively, states that we are still ignorant of the nature of the estrogen circulating in the blood. While the work of Venning and Browne[7] has been successful in providing us with the means of accurate assay of corpus luteum activity by pregnandiol levels, urinary and blood estrogen levels do not yield to the same accuracy of assay. Analyzing the urinary excretions reveals some information in that three separate fractions, namely, estradiol, estrone, and estriol, have been demonstrated.

and the relative levels of the excretion may be carefully assessed and compared in the pregnant and nonpregnant state. However, small variations in urinary estrogen in the nonpregnant state cannot be accurately assayed by the usual methods of study, and the urine represents only the excretion level which may not parallel the blood level. Heard[8] states further that only approximately 10 per cent of any estrogen injected into the intact body is recoverable in the urine. The vaginal cornification count provides a simple method of obtaining a reasonably accurate estimation of endogenous tissue estrogens, although it does not give the biochemical differentiation between estradiol, estrone, and estriol. Cornification counts may be made in a similar manner to a blood count. It is well known from cytology studies reported by De Allende, Shorr, and Hartman[9] and various other reliable investigators that the cornification level normally follows a cyclic pattern showing a rise from zero post menstrually, and rising gradually during the regenerative phase. There is evidence of slight day-to-day fluctuation which is probably dependent upon its variable production, metabolism, and excretion. A peak of cornification is reached at the ovulatory stage, and a physiologic drop occurs following ovulation. The curve during the secretory phase is somewhat more variable, but the usual premenstrual picture is one of very low or absent cornification.

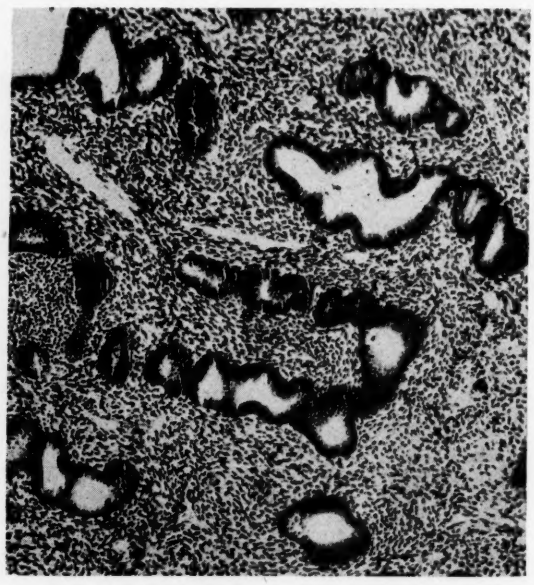

Fig. 3.—Endometrial biopsy in same case as in Fig. 2. The hyperactive proliferative pattern in a patient of this age confirms the presence of abnormally high estrogenic activity.

In humans and in monkeys the estrogens manifest their presence in the vaginal mucosa by a specific hormonal cornification change in the cells (first described by Allen,[10] associated with proliferation of the vaginal and cervical squamous epithelium. This growth change is related to the deposition of glycogen in the squamous cell which is mediated and controlled by the force of the estrogenic stimulus. The vaginal epithelium of the average postmenopausal female is thin and is made up largely of basal cells which contain no glycogen, and cornification is absent. Under the influence of the estrogenic hormone the deposition of glycogen may be brought about and cornification of the squamous cells occurs whether the subject be post climacteric or following oöphorectomy. This was demonstrated in monkeys by Robertson, Maddux,

and Allen[11] and in humans by Krumm.[12] We have confirmed the latter's observations in our own laboratory. When the cytology smears are stained with the Papanicolaou[13] stains (EA-50 and OG-6) using the technique perfected by him, the cellular picture is most colorful. The cornified cells stand out clearly and are recognized not only on the basis of their brilliant staining, but also on their morphologic characteristics. We have found further confirmation of the estrogenic activity by the study of the endometrium of senile patients suffering from cancer of the cervix. Many of these showing cornification in the smears also exhibited endometrium similar to that found in the regenerative phase in a young women (Fig. 3), while in other cases the estrogenic stimulus was sufficient to produce a picture of endometrial hyperplasia.

Studies of Cervical Tissue Estrogens

Our cytologic studies of the squamous epithelium of the cervix lead us to believe that this tissue reacts to the estrogenic hormones in a manner similar to that of the vagina, but with certain differences. The first and most significant is that this tissue exhibits a greater accentuation of the growth response induced by the estrogens. During the course of our cytologic studies we made the observation that the cervical cornification counts were found to be almost consistently higher than the vaginal cornification counts in the same cases. We had never been able to understand why this might be. During the course of a discussion, Dr. Edward C. Reifenstein of Memorial Hospital, New York, suggested the likelihood that estrogen may become concentrated in certain specific tissues. At the time, we wondered whether this was the explanation for the higher estrogenic cornification counts in our cervical smears. Later, in studying the experimental work of Brunelli,[14] we learned that in 1935 he had demonstrated that in rabbits estrogen present in the blood will become concentrated and fixed in inflamed tissues. This evidence suggests that chronic inflammation resulting from persisting infection in the cervical tissues might cause the concentration of estrogen in these tissues and thus account for the higher cornification counts. We therefore investigated comparative vaginal and cervical levels in a large series of cases, a report of which has been made elsewhere.[15] From a series of 125 cases studied without regard to disease, 87 per cent were found to show higher estrogen counts in the cervical smear than in the vaginal, and the average difference was 15 per cent. The conclusion from this study was that concentration of endogenous tissue estrogens may occur in this organ. Whether the endogenous estrogens are concentrated more in the cervix than in the vagina in all women is uncertain. The high frequency of occurrence of chronic cervicitis has led us to attempt to correlate cervicitis with the concentration of estrogen in the cervical tissues. In our opinion, probably all parous cervices and many nulliparous cervices have been subjected to a degree of cervicitis at some time during sex life and some residual disease doubtless remains in the glands as a chronic cervicitis. Such estrogen constantly influencing these infected tissues would tend to produce constant growth proliferation. A study of cervical tissue biopsies confirms this growth feature. While peripherally the squamous epithelium shows less cornification and is thin, approaching the squamocolumnar junction, the estrogenic cornified cells are more numerous, and the epithelium becomes thicker with more evidence of proliferation in the basal epithelium (Compare Figs. 6 and 7). Since growth activity is most pronounced approaching the squamocolumnar junction, it seems probable that infection in the glands influencing the squamous epithelium adjacent may exert an effect on the glycogen-estrogen metabolism in these "inflamed" cells. This seems a most significant consideration, in view of the great frequency of chronic cervicitis as a precursor of squamous carcinoma.

Equally convincing evidence that an estrogenic growth-stimulating factor is exerting its presence on the cervical epithelium is manifest in a study of biopsies of tissue adjacent to cancer growths (Fig. 2) in senile patients. The finding of a greatly thickened proliferative squamous epithelium with mature cornified elements at the surface is the same type of picture as may be induced by the administration of moderately large doses of an estrogen at any age, and is very much different from the thin atrophic epithelium found in normal postmenopausal cases.

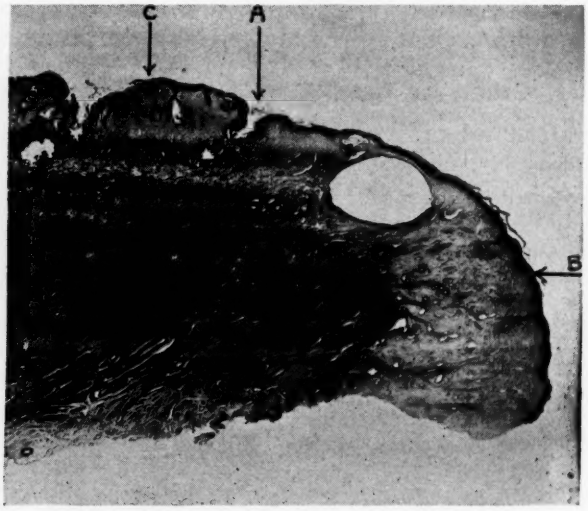

Fig. 4.—Cervical biopsy from young woman (30 years of age) complaining of intermenstrual bleeding. Pathologic diagnosis: cervicitis. Observe thickened squamous epithelium near glands which harbor infection.

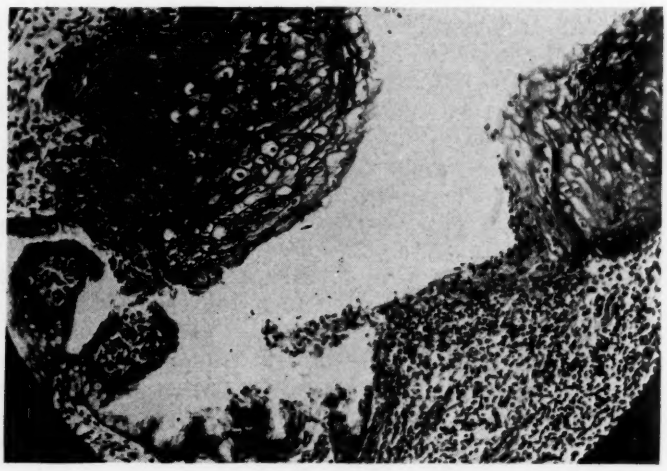

Fig. 5.—(High power of Fig. 4, *A*). Squamocolumnar area in same case showing inflammatory exudate in tissues, and hyperactive thickened squamous epithelium adjacent to infected tissues and glands.

Recent advances in the field of radioactivity may prove valuable in verifying our cytologic evidence of tissue estrogen concentration. It is our hope to attempt to trace the course of radioactivated estrogens when suitable isotopes become available. That this procedure is distinctly possible has been

shown by the work of Belanger and LeBlond,[16] and of others. Proof of fixation in the infected cervix will not only incriminate the growth-stimulating estrogens, but may offer better hope for successful treatment of cancer. The destructive rays given off selectively, where concentrated, might kill the sensitive neoplastic cells while undergoing mitotic division.

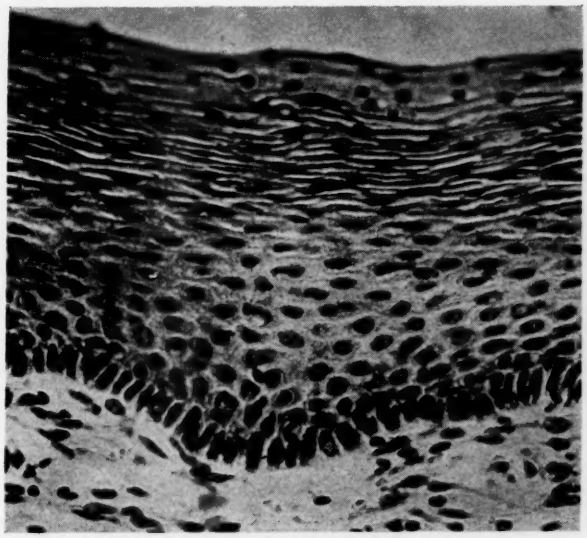

Fig. 6.—(High power study of Fig. 4, *B*). Biopsy of cervix peripherally, showing normal degree of proliferation.

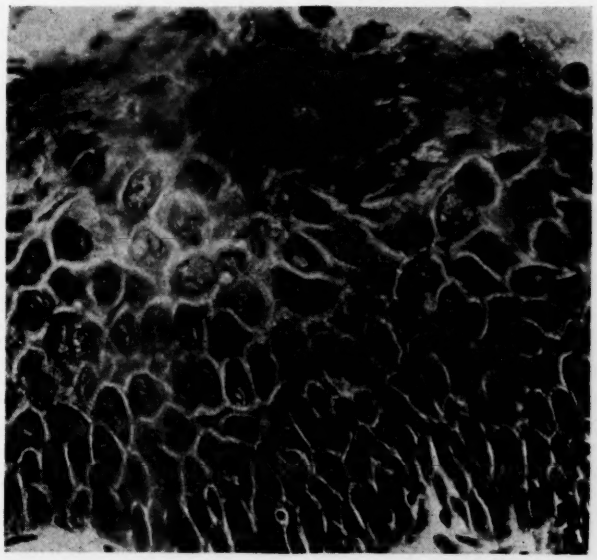

Fig. 7.—(High power study of Fig. 4, *C*). Biopsy of cervix approaching squamocolumnar junction in same case. Observe striking contrast in proliferative activity in region of infection. Cervical tissue estrogens excessive in cervical cytology smear. Note marked squamous hyperplasia with some loss of cell polarity.

An interesting correlation between thiamine deficiency, high estrogen levels, and gynecologic bleeding has recently been made in the three test cases referred to. This has led to investigation of a possible etiologic linkage

between nutrition and hormonal activity in association with cervical cancer. These patients were aged 14 years, 29 years, and 64 years, respectively. They were first studied in our gyne-cytology laboratory, all three of them showing abnormally high cornification during a bleeding phase. In addition, they presented other significant cytologic features. In view of the abnormal dietary habits revealed by their histories, urinary levels of the various vitamin fractions were undertaken. These have demonstrated low thiamine levels in all cases, while the other vitamin fractions were normal. A discussion of these cases individually follows:

CASE 1.—The patient, Mrs. M., aged 29 years, a nulliparous white woman of Anglo-Saxon extraction, was admitted to the hospital with complaints of severe menorrhagia of three months' duration, her periods usually lasting ten

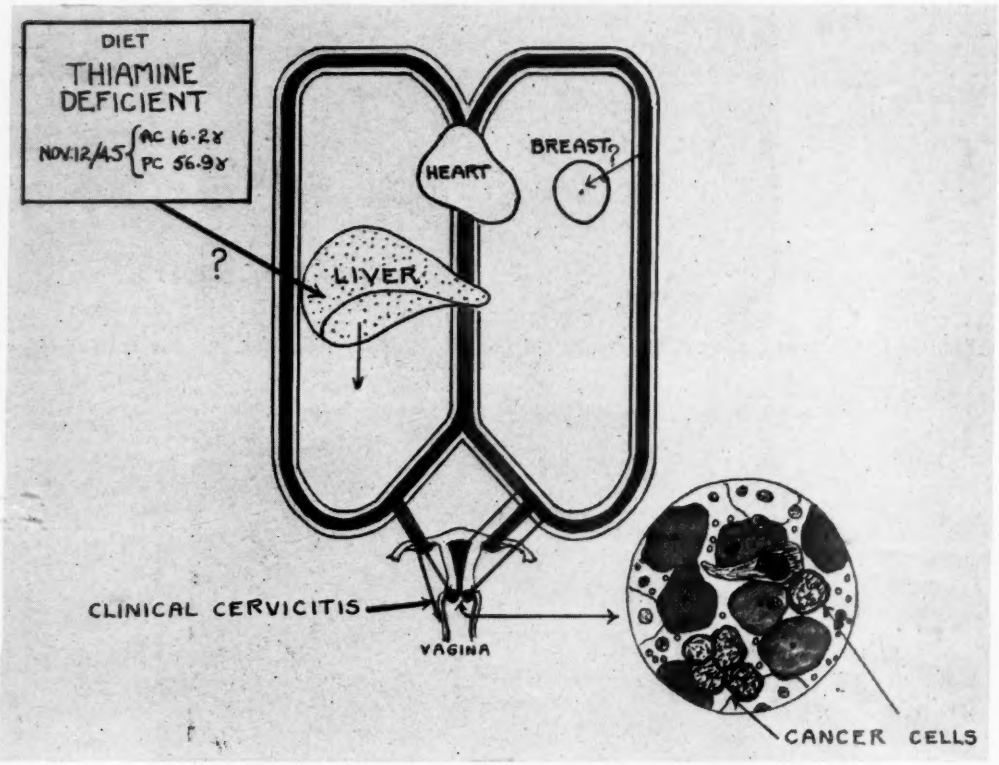

Fig. 8.—Human findings in early cervical cancer. Diagrammatic representation of diet-liver(?)-estrogen findings in Case 1 of early cervical cancer.

to fourteen days, with some intermenstrual spotting. She complained also of chronic constipation and severe abdominal cramps, aggravated by the taking of solid food, which at times produced nausea and vomiting. As a result the patient has been existing chiefly on soft foods and liquids, and stated that mineral oil was the only laxative she could take to stimulate intestinal action without inducing pain. It was revealed that she had for years partaken heavily of alcoholic beverages. In view of her obviously inadequate diet, it was felt that investigation should be made to determine a possible correlation between a nutritional deficiency and the severe menorrhagia. Pelvic examination revealed a normal-sized uterus with an inflammatory cervical erosion. Cervical cytology smears revealed two findings of note—the first a high cornification

level, the cornification count being 75 per cent, but second, and more startling, large numbers of cancer cells were also found.

At this time, estimation of urinary vitamin levels were reported by the Nutrition Department as follows: riboflavin—ac-188.4 (normal 165), pc-445.9 (normal 250); thiamine—ac-16.2 (normal 25-50), *pc-56.9* (normal 200).

Further biochemical examination gave the following results: nonprotein nitrogen 22.6 mg. per cent; total protein 7.56 mg. per cent; albumin 4.92 mg. per cent; sugar—ac-111 mg. per cent; pc-105 mg. per cent; bilirubin—direct 0.3 mg. per cent, indirect 0.8 mg. per cent.

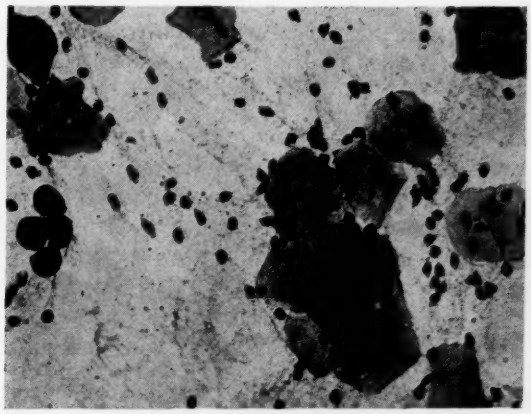

Fig. 9.—Cervical cytology smear (low power) of Mrs. M. (Case 1), showing excess estrogenic cornification count, cluster of neoplastic cells, leucocytes, and blood.

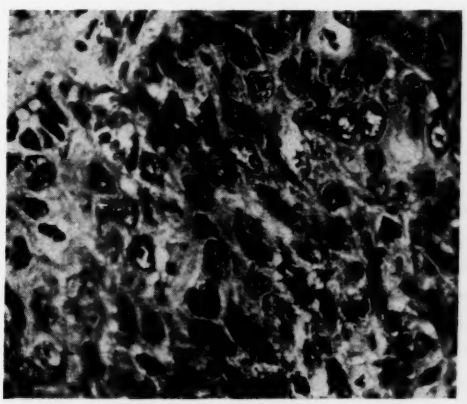

Fig. 10.—Cervical biopsy in Case 1 showing intra-epithelial carcinoma of cervix. This noninvasive lesion was invisible clinically. Patient showed cervicitis, high tissue estrogen (Fig. 9) and low thiamine etc., as represented diagramatically in Fig. 8.

Liver function tests showed: hippuric acid 1.3832 Gm.; bromsulphalein 2.4 per cent retention; cephalin flocculation—24 hours (+2), 48 hours (+2).

Blood examination revealed: hemoglobin 70 per cent; white blood count, 8,800/cu.mm.; sedimentation rate 40 (28 C.V.), compact cells 31.6 per cent.

Cervical biopsy for confirmation of diagnosis was undertaken. In view of the inability to detect any visually demonstrable lesion, several biopsies were taken and the uterine cavity was curetted. Following a study of serial sections of the biopsies, a localized carcinoma-in-situ was revealed.

Postoperatively, cytology smears continued to reveal profuse exfoliation of the malignant appearing cells.

Following consultation and discussion, a conservative course was decided upon, and the patient was merely subjected to a high cervical amputation. This very conservative surgery was performed with the intention of doing a panhysterectomy at a later date if any further evidence of malignant activity could be detected clinically or in cytology smears. Following the amputation of the cervix, smears have been taken regularly and at no time have atypical cells again been detected.

It is interesting that with no further treatment other than correction of her diet and bowel habits, and the administration of supplemental thiamine therapy orally, this patient has resumed a normal menstrual habit since the operation twelve months ago. While cytologic tests continue favorably, she is being followed assiduously with the intention of receiving further treatment with radium or surgery if indicated.

CASE 2.—Our first contact with this patient was made when her personal physician brought in cytology smears for a diagnosis of possible malignancy. He reported that his patient, a Jewish woman, 64 years of age, had recently noted a bloody vaginal discharge of two days' duration. She had had her normal menopause fourteen years previously. Study of the cytology smears showed malignant cells of the squamous type. In addition to this finding, the percentage of estrogenic cornified cells was abnormally high (42 per cent). On the basis of the patient's history, and the cytologic diagnosis of cancer, the patient was referred to Dr. W. A. G. Bauld, Chief of our Gynecologic Cancer Service.

On admission, examination revealed a well-nourished female with no complaints other than the history as given. Pelvic examination revealed a small indurated ulceration of the cervix which, from clinical evidence alone, aroused only a suspicion of malignancy to the experienced eye of Dr. Bauld.

Before any treatment was undertaken, the following biochemical estimations were made. The Nutrition Department reported urinary thiamine excretion as follows: ac-36.4, *pc-94.8*.

Biochemical examination gave the following results: nonprotein nitrogen 23.8 mg. per cent; total protein 5.6 mg. per cent; albumin 4.18 mg. per cent; globulin 1.42 mg. per cent; cephalin flocculation, negative; alkaline phosphatase, 4 units; bromsulphalein, 10 per cent retention; glucuronic acid, 3.85 mg. per cent of glucurone.

At operation, a confirmatory biopsy was taken and 4,800 mg. of radium were administered. The biopsy proved to be a squamous carcinoma of the cervix of a highly undifferentiated type.

In view of the low thiamine excretion level, the patient's dietary habits were investigated. It was revealed that while her financial status was good, her diet was average with the exception that very little meat was eaten and she admitted constant dieting to prevent overweight. The dietary analysis confirmed the inadequate thiamine intake.

CASE 3.—The patient, Miss N., aged 14 years, was a child of French-Canadian extraction, admitted to the hospital with the complaint of profuse vaginal bleeding of two months' duration. She had had her first menstruation at the age of 13 years, following which she had a period of amenorrhea of one year. A second menstruation occurred in August, 1945. She again started to bleed in October and this was continuous for two months, at times being quite profuse, and necessitating bed rest for two weeks prior to admission. Examination showed a frail anemic-appearing child, weighing 90 pounds, with slight breast development and incomplete growth of pubic hair. A striking feature

was noted in that the gums were toothless, a total dental extraction having been performed for dental caries two months previously. Pelvic examination revealed that the hymen was intact and the pelvic organs normal, though with an infantile tendency.

Following bed rest in the hospital there was no apparent diminution in bleeding.

Daily vaginal cytology smears were taken, showing a persisting high cornification plateau with clusters of endometrial appearing cells and considerable blood.

Biochemical examination gave the following results: Nonprotein nitrogen 20.4 mg. per cent; total protein 6.18 mg. per cent; albumin 4.02 mg. per cent; globulin 2.16 mg. per cent; bilirubin—direct 0.225 mg. per cent, indirect—0.55 mg. per cent.

Liver function tests showed bromsulphalein 2.4 per cent retention; cephalin flocculation 24 hours—negative, 48 hours—negative; hippuric acid 1.5115 Gm. Blood examination showed: hemoglobin 65 per cent; sedimentation rate—first hour 25 (C.V.9); white blood count, 8,900 per cu.mm.; prothrombin time, 36 seconds. Riboflavin was ac-190.0, pc-330.7. Thiamine was ac-11, *pc-51.*

This patient was treated further by having a curettement following completion of her biochemical studies. At the time of the operation, the pelvic organs were found to appear normal. When the uterine cavity was explored, a large quantity of thick endometrium was evacuated, and parts of this appeared to be grossly firm and polypoidal. Following operation, the patient was placed on large daily doses of thiamine.

Pathologic study of the tissue removed showed numerous endometrial polypi with marked glandular hyperplasia and slight cystic change in evidence. Parts of the gland tissue presented an appearance of growth of an adenomatous character. Indeed, the pattern was such that if the patient had been 40 years of age instead of 14, the tissue would have been considered carefully before dismissing borderline malignant change.

This patient has resumed a normal menstrual cycle during the past eighteen months on a corrected dietary regime supplemented by adequate doses of vitamin B complex.

Liver Studies in Animals

Certain evidence has already been presented in animal studies to show that liver damage sufficient to interfere with the excretion of the estrogens does occur.

Biskind and Biskind[17] reported that vitamin B complex deficiency interferes with estrone inactivation in the liver in female rats. They implanted pellets of estrone in the spleens of adult castrated female rats. The estrone must pass directly to the liver by way of the portal circulation before reaching the systemic circulation. While these animals were fed a normal stock diet, no estrus developed. When the diet was changed to one totally deficient in vitamin B complex, it was observed that within two weeks on this diet, irregular estrual changes began to occur. This was interpreted as indicating that the estrone was not being completely inactivated, and after three weeks on this diet, the rats remained in a state of constant estrus.

Since this time numerous investigators have confirmed the observations of Biskind and Biskind.[17] Segaloff and Segaloff[18] found that a deficiency of the B vitamins decreased the ability of the rat's liver to inactivate estrone, alpha-estradiol, and diethylstilbestrol, as indicated by an increased vaginal response to intrasplenically-injected estrogen. When either thiamine or riboflavin were administered in large doses, the rate of inactivation of estrone and alpha-estradiol (but not of diethylstilbestrol) returned to a normal level.

Singher, Kensler, Taylor and others[19] reported their observations of liver inactivation of estradiol when the following specific deficiencies were produced, viz., thiamine, riboflavin, pyridoxine, pantothenic acid, biotin, and vitamin A. Using liver slices of rats and mice, their observations indicated that estradiol inactivation by the liver depends on the liver content of riboflavin and thiamine. The levels of pyrodoxine, pantothenic acid, biotin, and vitamin A in the liver had no influence on the inactivation of this estrogen. They concluded that thiamine and riboflavin are essential in the metabolism of estradiol by liver slices, and they state that it seems possible that these vitamins may be involved in estrogen metabolism through their role as members of an oxidative enzyme system. Zondek[20] reported that the liver is capable of inactivating from 80 per cent to 90 per cent of added estrogen in vitro.

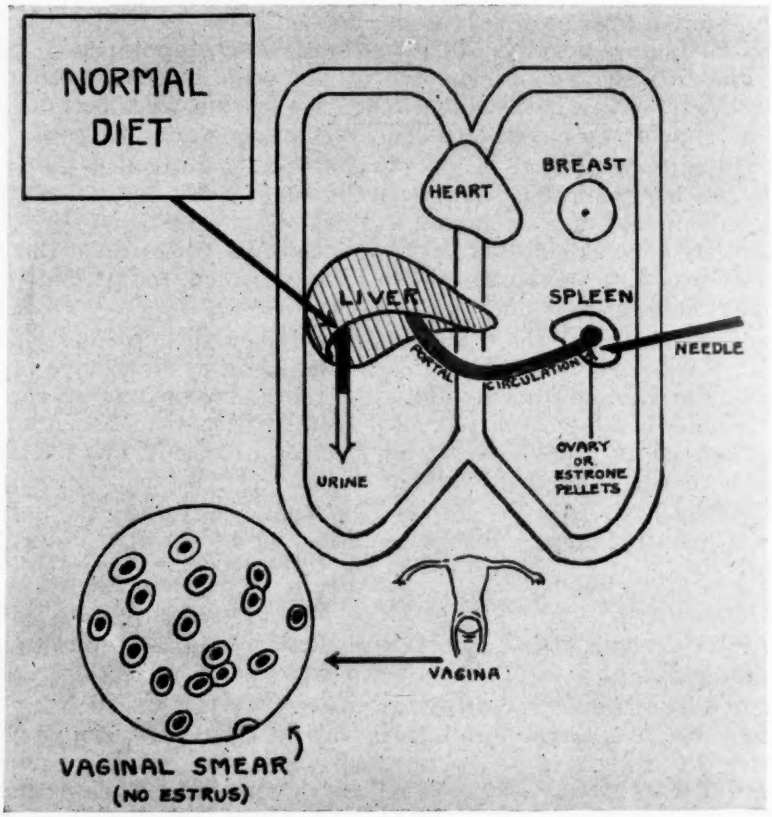

Fig. 11A.—Experimental intrasplenic estrogenic administration to castrate female rats. Diagram illustrating experimental evidence of nutrition-liver-estrogen inter-relationship in animals. Estrogen from the spleen enters portal circulation travelling direct to the liver. In Fig. 11 *A* with normal liver function the liver inactivates the estrogen and no estrus develops.

Golden and Sevringhaus[21] transplanted rat ovaries to the mesentery and to the axillae. Estrus did not occur in animals with ovaries in the portal circulation, but did occur in those with transplants in the axillae.

Talbot[22] extended the observation of Golden and Sevringhaus[21] on destruction of endogenous estrogen by demonstrating that a liver poison, carbontetrachloride, can impair the estrogen-inactivating mechanism.

It has been recognized that menorrhagia and metrorrhagia may occur early in the course of cirrhosis of the liver,[23] and the work of Gyorgy and Goldblatt,[24]

and of others has demonstrated that cirrhosis of the liver is known to result from nutritional deficiency. Sources of the B complex have been shown to protect the liver against a variety of toxic agents such as lead, arsenic dimethylaniloazo-benzene, which cause functional and morphologic damage to this organ. In addition to this evidence, Goldberger[25] has shown that menorrhagia may occur in pellagra.

In 1940, Glass, Edmondson, and Soll[26] reported that in male patients with cirrhosis of the liver the estrogen in the urine appeared in active form. Gynecomastia and testicular atrophy were associated with the excess of free estrogen.

Estrogen as a Carcinogen

Whether or not the accumulation of uncertain quantities of estrogens in the body would act as a carcinogen to the estrogen-susceptible tissues of the Müllerian tract and possibly the glands of the breast, is worthy of consideration.

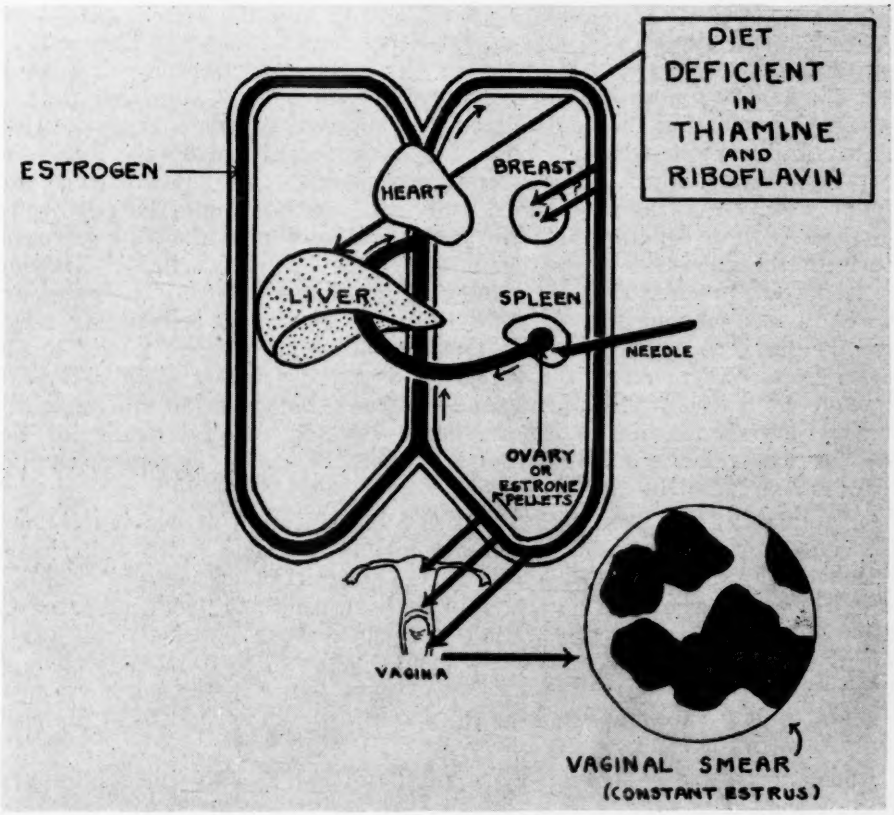

Fig. 11 *B*.—Experimental intrasplenic estrogenic administration to castrate female rats. Diagram illustrating experimental evidence of nutrition-liver-estrogen interrelationship in animals. Estrogen from the spleen enters portal circulation travelling direct to the liver. In Fig. 11 *B* constant estrus develops.

References: Biskind, M. S., and Biskind, G. R.: Endocrinol. 31: 109, 1942. Segaloff and Segaloff, Endocrinol. 34: 346, 1944. Singher, H. O., Kensler, C. J., Rhoads, C. P., et al., J. Biol. Chem. 154: 79, 1944.

It is known that estrogen is essentially a growth-promoting hormone affecting the uterine and vaginal tissues and, to a lesser extent, the mammary gland. During a normal cycle the endometrium manifests the most rapid physiologic proliferation during the follicular phase under the influence of an increasingly

great secretion of estrogen leading up to the time of ovulation. Its effect is also specifically exerted upon the squamous epithelium of the vagina, and a comparable manifestation of growth may be observed in this tissue coincident to the endometrial changes. The uterine cervix is covered by the same type of epithelium and reacts to the same growth stimulus, and this is the tissue most commonly involved in cancer in the human female.

Pincus and Graubard,[27] in studying estrogen metabolism in seven women suffering from cancer of the uterus, concluded that these cases metabolized the estrogen in an abnormal manner. While noncancerous women showed a definite increased total estrogen output (in the urine) following administration of estrone plus progesterone, the cancer cases showed a negligible increase in the urine after the same treatment. The fact that the estrogen was not excreted the same as in a nonmalignant case suggests more profound liver impairment.

The administration of estrogens to certain animals has been followed by the development of various types of neoplasia.

A recent survey of evidence of estrogenic activity in 62 granulosa-cell tumors has been made by Hodgson, Dockerty, and Mussey.[28] They cite "evidence of hyper-estrinism is afforded in our series by symptoms of precocious puberty, amenorrhea, and postmenopausal bleeding" and observed that "urinary assays performed in the case of a woman, aged 57 years, were positive for eight rat units of estrogen per liter of urine excreted during the first twenty-four postoperative hours. The excretion of estrogen dropped to zero during the next twenty-four hours. Blood and urine assays should be performed in these cases both preoperatively and postoperatively to widen our information concerning the excretion of estrogen as well as to aid in clinical diagnosis." They reported proliferative endometrium in 67 per cent of their cases. In thirty-eight postmenopausal patients who had granulosa-cell tumor they reported 21 per cent as showing endometrial carcinoma and, in almost one-third of these cases, carcinoma of the breast with axillary metastasis also developed. They concluded that "this phenomenon of coexistent ovarian endometrial and mammary carcinoma in the human being bears a marked similarity to the results of experiments on laboratory animals in which estrogen stimulation appears to be a factor in carcinogenesis."

In animals it has been found that the implantation of ovarian tissue produced cancer of the breast in cancer-susceptible mice and it was felt that some secretion of the ovary played a role in the production of cancer. For a long time it has been recognized that certain coal tar products produced cancer with greater certainty than any other known chemical or physical irritant. The chemical structure of such substances has been found to contain benzene rings linked together. Certain active substances were found in the sex hormones, the bile acids, and in cholesterol exhibiting a similarity in structure to the coal tar preparations.

Rhoads[29] has presented evidence to show that in rats the administration of one of these two-benzene-ring substances, "butter yellow" will result in the development of cancer when their diet consisted of polished rice and carrots. It was found that if liver or yeast was added to the basal diet, no cancer occurred. Here, clearly, was an experiment in which a dietary constituent, rich in its content of the vitamins of the B complex, was protective against induced cancer. In studies of the vitamin B content of cancer tissue, it has been shown that the tissue of human, as well as of mouse carcinoma, is low in its content of vitamin B. This was reported in 1929 by Jackson and Kranz.[30]

Extensive studies on numerous experimental animals, including monkeys, indicate that prolonged and not necessarily excessive administration of estrogens may produce changes in the epithelial structures which they normally stimulate,

that is, mammary, endometrial, and cervical epithelia, which vary from benign hyperplasia to definite malignancy.

Gemmel and Jeffcoate,[31] in 1939, reported three cases of carcinoma of the cervix in a series of more than forty cases of senile vaginitis and kraurosis vulvae treated with estrogens.

Auchinloss and Haagensen[32] in 1940 reported a case of mammary carcinoma with axillary metastasis in a woman treated for menopausal symptoms for over a year with moderately heavy doses of estradiol benzoate. They believe that in this case the cancer was probably produced by the estrogen in a woman with a definitely bad family history.

J. S. Henry,[33] in a recent extensive survey of the role of estrogen in carcinogenesis, reports two cases of endometrial overgrowth of a malignant or precancerous nature in women who had taken an estrogen continuously over a prolonged period of time. He considers it probable that the changes found in these cases were produced by the estrogen therapy, and wisely counsels that prolonged or excessive administration of these hormones in practice should not be undertaken without careful consideration and knowledge of their potentialities. From the evidence presented, it would appear that the administration of estrogen may be harmful in those cases where obscure liver damage might have followed a dietary deficiency or some other damaging influence.

Method of Investigation

1. *Cytology.*—Cytology tests were taken from the cervix using the method described by Ayre and Dakin.[34] The secretions aspirated from the external os of the cervix presented evidence, first, as to the diagnosis of cancer, and second, by careful cornification counts of the cellular elements, endogenous estrogen levels were assayed. In those cases of advanced carcinoma, and in the cases of hemorrhage where the quantity of blood or purulent material obscured the cornified elements, a special technique was used for the cornification estimation. Using a speculum, a small spatula was employed to scrape the smooth mucosal surface of the cervix peripheral to the growth, thus avoiding the thick admixture of mucus, leucocytes, and blood on the surface of the growth and covering the vaginal floor. This permitted, we feel, a more accurate estimation of the estrogenic cornification. The fifty cases of cancer in this present investigation were studied using this technique while the preceding 150 odd cases were studied using the older method. We feel that this improved technique accounts for the higher percentage found to exhibit abnormally high cornification levels. The spatula technique has proved invaluable in the diagnosis of microscopic cancer, as the cells exfoliated precisely from the squamocolumnar junction may be scraped up in this selective fashion and smeared on the slide. This new technique has been described elsewhere.[35]

2. *Nutrition.*—The nutrition studies were made by Dr. W. A. Andreae of the Nutrition Department of the Medical Laboratory of McGill University Clinic. It is noteworthy that the biochemists in the Nutrition Department had no knowledge or information of which specimens were from cancer cases, and which were from controls, before the results were computed. The vitamin status in the present investigation was estimated by a vitamin tolerance technique. Following a vitamin-free supper, the night urine from 12 midnight to 8 A.M. was collected in a bottle containing acetic acid. In the morning, after a vitamin-free breakfast, an intramuscular injection of 1 mg. thiamine and 1 mg. riboflavin was given and the urine collected for the subsequent four-hour period. Both specimens were analyzed—by the thiochrome method of Wang and Harris[36] for thiamine, and by the Ferrebee method[37] for riboflavin. Patients with below normal excretion values were classed as deficient in thiamine and/or riboflavin.

The results of thiamine and riboflavin tabulated in the charts below are taken in each case from the pc. reading.

3. *Liver Function Tests.*—Through the cooperation of Dr. M. M. Hoffman, liver function tests were attempted in those cases who were available for this type of investigation. Unfortunately, the number of patients undergoing this study was small, and the results are therefore inconclusive. The cephalin flocculation test and the bromsulphalein tests showed more consistently abnormal readings than other liver tests.

4. *Urinary Estrogens.*—Urinary assays of estrogen were attempted in a few cases. Most of the patients, however, were not readily available for this type of study, and it was felt inconclusive to attempt these arduous studies without adequate control over the subjects. For accurate studies the entire urinary output over a considerable period of time would require analysis, and a single 24- or 48-hour quantity would not be conclusive.

Nutritional Studies

It perhaps seems remarkable in these days of scientific enlightenment and dietary refinement that deficiency would occur irrespective of the economic status of the patient. It has long been a general feeling among gynecologists that dietetics were not directly concerned with the production of pelvic pathology, and that the need for vitamins in particular was generally overstressed. It would seem logical that the average person with a normal appetite for the various staple foods should not develop a deficiency due to an inadequate intake. A study of thiamine physiology and metabolism reveals evidence to indicate that this substance would appear to be particularly vulnerable to intermittent or chronic depletion without gross deficiency in the diet as a whole. This tendency would appear to depend upon the fact that little thiamine is stored in the organism, and the amount is only sufficient to maintain proper life for a few days. A daily intake of thiamine is necessary, and the organism absorbs only enough for the immediate needs. The excess is destroyed or excreted. More is required when a high carbohydrate diet is taken or when alcohol is imbibed. We have found that a vicious cycle may develop as anorexia and constipation frequently develop in the presence of even a mild deficiency. Therefore, the more persistent the anorexia, the more chronic the deficiency becomes.

This vicious cycle would appear to be of more than passing importance. A discussion of dietary habits with some of our patients found to have a low thiamine excretion level has proved most illuminating. Some of these patients when questioned have admitted a diet consisting of tea and toast and potatoes, and when asked why they did not eat more, they indicated that they had no appetite and had almost to force themselves to eat what they did. Chronic constipation is consistently present and loss of weight has not been uncommon. Chronicity appears to be the rule once these patients slip into this rut. In an effort to determine whether the thiamine excretion level may have been only a transient deficiency, repeat tests have been done from month to month on certain cases without alteration of diet. These cases have most consistently shown a persisting low level over a period of several months. On the other hand, by simple correction of diet, the excretion levels have been normalized within an interval of seven days. The majority of these patients have not exhibited the appearance of undernourishment. On the contrary, most of them were a little overweight and, in addition, showed a lowered basal metabolic rate. Indeed, many of the patients admitted constant dieting in an effort to keep their weight down. This usually signifies a low fat intake which would seem to be one of the possible reasons why such patients would develop the thiamine deficiency, as the lower the fat intake, the greater becomes the body requirements of

thiamine. Therefore, it would seem that two different types of dietary errors might predispose to thiamine depletion—those who are living on sweets and starches, and those who are constantly dieting to prevent or minimize obesity.

Thiamine is a water-soluble substance which is absorbed in the small intestine and is partly secreted in the gastric juice. It is stored in certain organs, namely, the kidney, liver, and heart, in small but variable amounts. It seems surprising that pork muscle contains eight times as much as beef.

Thiamine is important in carbohydrate metabolism. Glycogen requires its presence to be properly metabolized. Thyroxin secretion increases general metabolism and therefore necessitates an increased amount of B_1. The thiamine requirements are variable. More is needed in pregnancy, in hard physical labor, or with increased metabolism. A diet rich in fats reduces the amount of thiamine needed. In general, the daily minimal requirements are 50 to 300 international units.

A deficiency of thiamine can be accurately detected by measuring the amount excreted in the urine. A normal person excretes 100 micrograms per day.

With so much discussion of vitamin therapy nowadays, one might be led to believe that they are a "cure-all." The truth, however, is that vitamins are only nutritional elements, and to say that a vitamin would cure a deficiency or a disease resulting from a deficiency, is simply to say that a well-balanced diet, properly absorbed and utilized, would have prevented the disorder.

Results

A group of 100 gynecologic cases manifesting evidence of malignancy or normalcy have been studied cytologically for evidence of estrogenic activity in the gyne-cytology laboratory and nutritionally by thiamine excretion assays performed in the Nutrition Department of the Medical Laboratories of the McGill University Clinic. The series is made up of 50 cases of cervical cancer. Fifty controls were studied concurrently by similar vitamin-hormone assays. These controls were selected on the basis of normal gynecologic health, both subjectively and objectively, patients of a similar age group to the cancer series being selected wherever possible. The results have been shown graphically in Table I.

TABLE I

	HIGH CORN. LOW THIAM.	HIGH CORN.	NORMAL AND LOW CORN.	NORMAL THIAM.	LOW THIAM.
50 Cancer	82%	92%	8%	14%	86%
50 Controls	0	6.2%	94%	90%	10%

Results of Riboflavin Estimations

Total number of cases studied	100
% of cases having riboflavin test	80%
% of low riboflavin in 38 cases of cancer	36.8%
% of low riboflavin in 42 control cases	6.8%

Explanation

The thiamine excretion level used by Dr. W. A. Andreae of the Nutrition Laboratory to denote deficiency of thiamine is 200 α during the four-hour period following the injection of the 1 mg. test-dose of thiamine parenterally. For the purpose of this investigation 175 α has been chosen as the arbitrary level for normals in order to eliminate borderline cases. In the majority of the cases, riboflavin levels were also investigated. It is unfortunate that lack of adequate laboratory assistance made it impossible to measure this function in all cases.

Abnormal endogenous estrogenic activity has been interpreted by cornification counts in vaginal and cervical smears. The degree of abnormality represented by plus or minus takes into consideration the age of the patient and the stage of the menstrual cycle. Whether the cornification count is slightly elevated above normal, or is marked, is indicated by degrees, viz., one, two or three plus. "N" represents normal expectations, and minus represents a lower than normal cornification level.

Analysis of Results

Chronicity or variability of all three factors under consideration must be borne in mind. The infection is chronic and probably does not vary appreciably from month to month. Blood estrogens normally are believed to vary in a cyclic fashion. This may be greatly changed by liver dysfunction. Tissue estrogens, on the other hand, may be more constant due to fixation. Thiamine excretion might be expected to vary with the diet. While the intake of thiamine in the diet of most people would tend to show some variation from week to week,

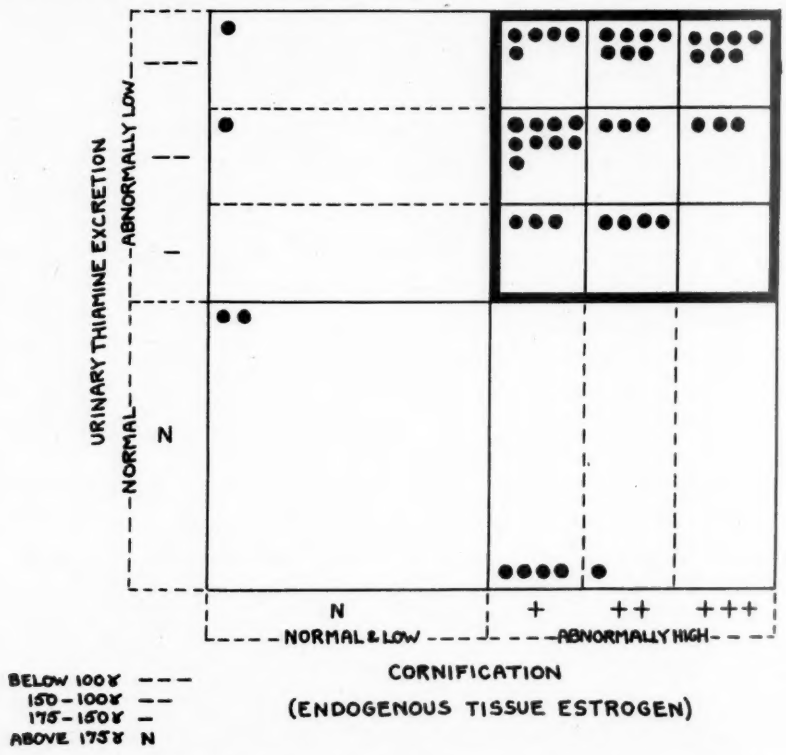

Fig. 12A.—Graphic representation of thiamine-estrogen findings in 50 cancer cases.

dietary habits and errors of habit do show a tendency to chronicity, and, as we have indicated elsewhere, once these patients have slipped into the rut of deficiency, the vicious cycle resulting may tend to keep them there, and in the patients on whom repeat levels were taken over a period of months, chronic deficiency was demonstrable. The tissue estrogens might also tend to show some variation. Primarily, the blood estrogen level, and secondarily, the urinary and tissue estrogens, would depend upon variable production, metabolism, and excretion. According to our presently discussed evidence, the metabolism and excretion might vary with the diet and liver function, and also with infec-

tion in the cervix. If infection does cause a fixation of estrogen in the cervical tissue, the degree of stability of this fixation would also influence excretion levels. It may also help explain the finding of excess tissue estrogens in postmenopausal cancers. If the estrogen is firmly bound in these cells, the blood and urine estrogens might disappear entirely, while that in these tissues might remain. It is uncertain at our present stage of incomplete knowledge how much the concentration of estrogen in cervical tissues may depend upon changes in systemic levels and how much upon local changes. There are two possible considerations. First, the systemic changes which may result from the nutritional deficiency, liver dysfunction, and resultant estrogen accumulation in the blood. On the other hand, the purely local fixation and concentration of estrogen in the infected cervical tissues must be considered. Probably both mechanisms

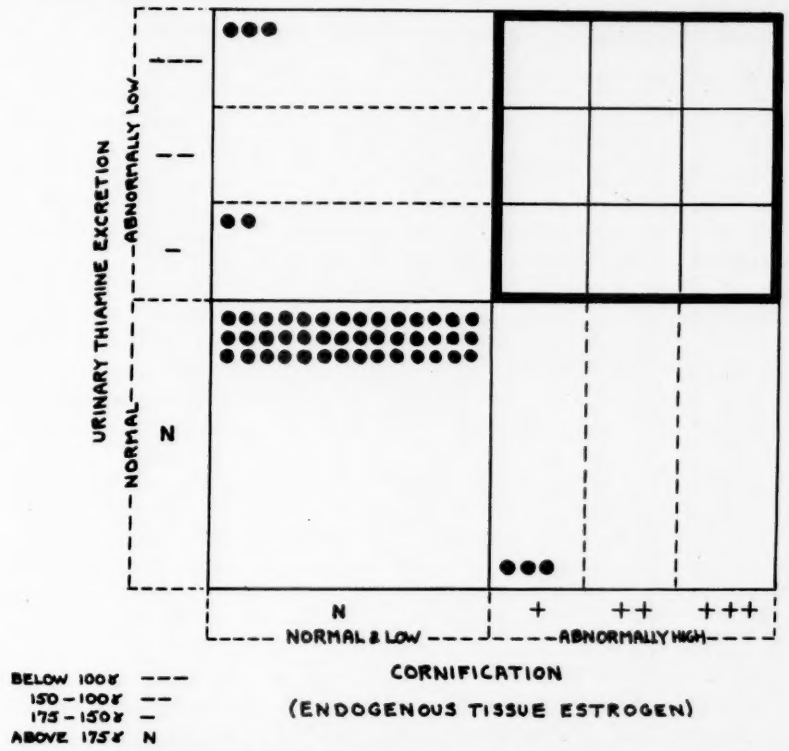

Fig. 12*B*.—Graphic representation of thiamine-estrogen findings in 50 control cases.

are active, the systemic changes probably varying considerably depending upon the variable dietary intake, the production of estrogen, and its accumulation in the blood. It seems likely that changes in estrogen blood levels might be rapid and considerable. The tissue estrogens in the cervix would also tend to rise with the availability of more estrogen from the blood, but it might not fall as quickly due to the tissue fixation. Such a mechanism would offer at least a partial explanation for the finding of evidence of abnormally high tissue estrogens in postmenopausal or senile women suffering from cervical carcinoma. While the blood may be subject to transient elevations in the estrogen level produced by either a temporary rise in production by the ovary or possibly the adrenal, or by a possible liver block which leads to temporary accumulation of even small traces being produced—such elevations of estrogen though transient might permit the concentration of these estrogens more permanently in the cervical tissue exerting affinity toward this substance.

The thiamine deficiency may also exert a dual role, acting on the liver, but also acting locally upon tissue cells in such a manner as to affect the metabolism and growth character of the individual cells of the cervix.

The fact that thiamine deficiency exists does not per se imply that the estrogen will be high and, therefore, that a cancer-potential exists. Ten per cent of the controls were thiamine deficient but they did not show high estrogen. This confirms that estrogen production is independent of the nutrition status, except possibly in acute starvation where menstruation and ovarian function may cease. This suggests, too, that the absence of the estrogen might nullify the neoplastic hazard.

It must be remembered that the cases we have analyzed have not been starvation victims, but rather, mild, probably chronic deficients. A statistical survey of cancer incidence in Europe during the next few years might yield valuable information if the machinery were available to collect accurate records.

Whether the low thiamine levels signify a pure deficiency of this nutritional element, or whether they signify a more general nutritional deficiency state of which the low thiamine is only an indicator we cannot be certain. Some evidence points to a pure thiamine deficiency. Most of our cases analyzed for vitamin A and vitamin C levels have shown normalcy in these respects. While our riboflavin results are incomplete, those available, which include 80 per cent of our series, tend to indicate that riboflavin occupies a secondary position in frequency of depletion and probably also in velocity to thiamine. While the majority of cases have shown a mild or moderate thiamine deficiency, usually only the moderate or severe cases have revealed a drop in the riboflavin level. Of our total series of cancer cases, 36.8 per cent have been shown to be deficient in this vitamin factor. In attempting to correct thiamine and riboflavin deficiencies by improved diet alone, our cases have shown further that the thiamine level is recovered more quickly than the riboflavin.

Chronicity is an unknown factor, but recent findings in early microscopic cervical cancers point to a long period of development, probably several years. Most people develop a fixed habit of diet, and a dietary error over a period of time would tend to produce a chronic deficiency. Chronicity would seem to be the rule, too, in regard to the infection and to the persisting estrogen stimulation.

While there are still many unknowns in the enzymic activity of thiamine and riboflavin as related to body and tissue metabolism, liver function and estrogen metabolism, the frequency of the reported combination of findings would appear to be more than coincidental. It has long been recognized that chronic irritation is a contributing factor leading to the development of many types of cancer. It is accepted knowledge that infection alone will not produce a malignant growth without the addition of other unknown factors. It would appear that both nutrition and estrogen have a role to play. Undoubtedly, the precise intensity, chronicity, and selectivity of all three elements must exert a fundamental force upon body tissue and cell metabolism, and these factors are still obscure.

It was mentioned in the previous publication[5] that even while the thiamine-estrogen hypothesis was still on the proving ground, it was possible to use the two tests: (1) the cytology test (a) to detect uterine cancer, or (b) to detect abnormally high cornification, and (2) to check the thiamine level. It was stated that even in the absence of cancer cells, the demonstration of a linkage of high cornification and low thiamine constituted a possible precancer indication which might be corrected. Since this time, and following a routine cytologic investigation of the cervices of a large group of several hundred women with no definite gynecologic complaints, cytologic evidence and biopsy

confirmation have been found of microscopic preinvasive carcinomas in a surprisingly large number of cases. It is of interest, and probably also of significance, that these patients appear clinically to be in good gynecologic health with the exception that they show signs of the so-frequent chronic cervicitis. Yet their squamous cells scraped from the squamocolumnar junction of the cervix[35] show evidence of neoplastic changes in addition to abnormally high tissue estrogens. These patients have also shown the same high consistency in their deficient thiamine excretion levels.

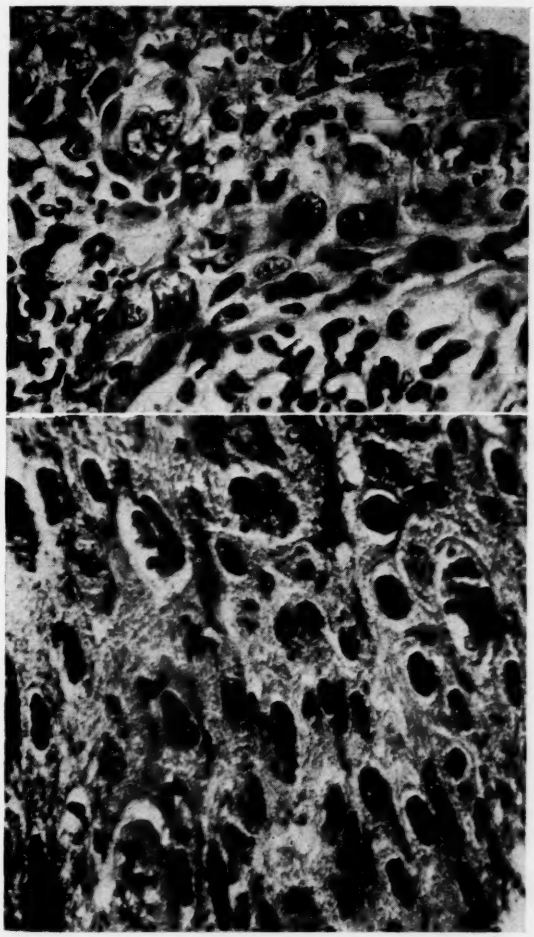

Fig. 13.—Pathologic study of cervical growth under high power. Observe numerous mitotic figures and large malignant-appearing cells. Two different pathologists have diagnosed this growth as carcinoma. Was this cancerlike growth induced in this 25-year-old patient by the administration of estrogen while nutritionally deficient? Inflammatory exudate throughout sub-epithelial tissues (Fig. 14) is apparent.

These cases proved instructive, firstly because they may be considered to be "cancer-in-the-making." The lesions are minute and no secondary influence upon general body nutrition was apparent. Cachexia was totally absent, and any possible reverse toxic action (if any occurs) of a large malignant growth upon the liver and body metabolism was absent. Symptomatically, most of these patients complained of mild gastrointestinal disturbances with loss of appetite and constipation and occasionally some loss of weight. Gynecologically, leucorrhea, menorrhagia, and occasional intermenstrual spotting

of blood were noted. These patients have shown in general a low basal metabolic rate of –10 to –20, while they have exhibited a normal blood picture. In other words, these cases of beginning-cancer show the same evidence of our theoretical carcinogenic mechanism as the more advanced lesions. This fact would seem to be significant because forces in the body controlling growth which become disordered in some specific manner to produce a growth of a

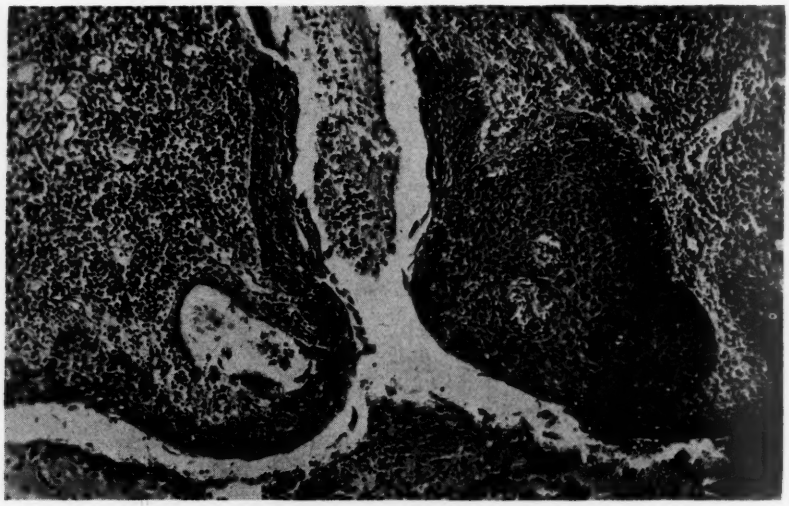

Fig. 14.—Low power of same growth as shown in Fig. 13. Note infected glands and tissues.

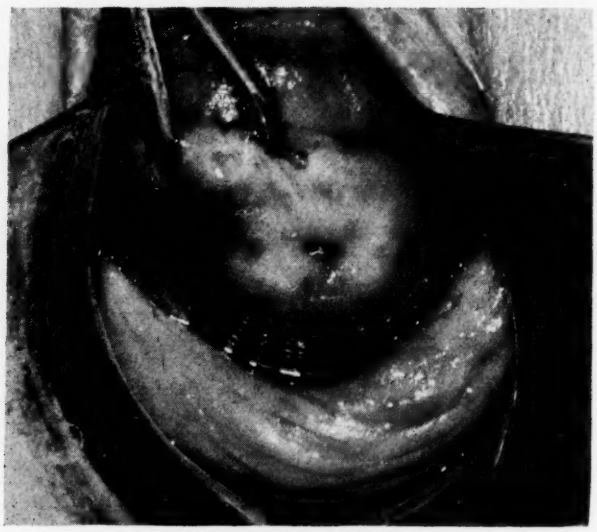

Fig. 15.—Clinical appearance of cervix in same case at the present time.

malignant nature—these forces are not necessarily fixed in their intensity and chronicity. Recent comparative studies of rates of growth in a preinvasive as compared to invasive carcinoma of the cervix reveal most interesting and hopeful evidence of two separate rates of growth activity in the preinvasive, silent stage as contrasted with the invasive clinically demonstrable stage. Evidence has been reported elsewhere[38] that a long interval of from one to eight years, or longer, may elapse between the preinvasive and the invasive stage of

cervical squamous carcinoma. At some point during this interval, a definite change occurs. Whether this is due to a change in force, intensity, or chronicity of the factors under consideration is not certain. Some gynecologists have argued that a change may also occur in the opposite direction, i.e., to produce a regression and spontaneous disappearance of the lesion rather than a progression to clinical carcinoma. While it is fascinating to dwell upon this prospect, evidence to date has revealed numerous cases to show that invasion ultimately does occur, while no evidence has as yet been reported to show that the reverse may happen. This remains as an interesting possibility for further investigation. Whatever particular combination of forces may initiate an invasive cancer, is probably not the same combination of forces which may act to sustain this growth, once fully established. We know that once full-blown, invading carcinoma becomes a reality, it becomes totally independent of all body controls, and from this point onwards it would doubtless continue in its uncontrollable growth habit regardless of a diminution of whatever growth-stimulating factors may have produced it.

Induced Cancer of Cervix?

The administration of an estrogen (stilbestrol) to a 25-year-old patient showing chronic cervicitis and a low thiamine excretion level was followed by the appearance of a cancerlike growth at the squamocolumnar junction (Figs. 13, 14 and 15). This patient complained only of leucorrhea, fatigue, and constipation. The administration of estrogen in moderate doses over an interval of ten weeks was followed by vaginal spotting of blood, and cytology tests revealed cells of malignant morphology. Complete excision of the squamocolumnar circle of the cervix revealed the lesion as shown. Details of this case have been reported elsewhere.[39] The appearance of the cervix six months following surgical excision with the electro-cautery is shown in Fig. 15. The cervix appears normal, and no further evidence of disorder is detectable, clinically or cytologically.

Human Liver Function Studies

While most authorities agree that liver function tests in human beings leave much to be desired, some progress has been made by certain investigators toward assessing various functions of the liver on the basis of the available liver function tests. Dr. M. M. Hoffman of the Medical Laboratories of the McGill University Clinic, who has studied liver function tests intensively, states that no single test has as yet been elaborated to assess liver damage, and it is possible to have liver damage sufficient to interfere with estrogen inactivation without this damage being detectable by the tests at present at our disposal. However, some attempt has been made by us to gain what information might be available in this regard in certain of our cancer cases, and whenever our cancer patients were accessible for liver function study certain tests were taken. The results of these are presented in Table II.

TABLE II. LIVER FUNCTION RESULTS—CANCER CASES

Number of cases having liver function test	20
Number of these cases showing low thiamine	20
Number of cases showing abnormal cephalin flocculation or bromsulphalein readings	11
Per cent showing abnormal liver function tests	55%
Number of cases having liver tests before and after correction of thiamine deficiency	6
Number of cases showing correction of abnormal liver reading after thiamine therapy	6
Per cent showing corrected reading	100%

It was considered to be of some significance that 18 of 22 of our cancer cases tested showed borderline or abnormal function as indicated by the bromsulphalein or cephalin flocculation tests. While we must consider that liver impairment may result from some toxic substance elaborated by the malignant growth, this would hardly seem to be the explanation in lesions of microscopic size. Of passing interest is the fact that of the cases showing this evidence of impairment, all of them at this time showed deficient thiamine excretion. Following the administration of thiamine chloride orally and parenterally to six of them, definite change in the liver function reading was noted within seven to ten days. The abnormal liver function reading in all six of these cases had changed to a normal reading. No other change in the regimen in these cases could be determined, which might explain this improvement. The clinical improvement in cancer cases, regardless of stage, is striking. Following correction of nutritional defects, these patients lose some of their cachetic appearance and show improvement in appetite. Some of them have, over a period of months, improved dramatically, gaining as much as twenty to thirty pounds in weight. It has been observed, too, that patients receiving thiamine or B complex in large doses during the course of x-ray or radium treatment, have exhibited a greatly reduced degree of the usual radiation sickness. Such clinical changes might be expected in the presence of a deficiency. But the change in the liver function readings may be of some significance. While the small number of cases studied for liver function permit no definite conclusions, the leads established demand more intensive investigation.

Speculation on Nature of Cancer Production

Is squamous cancer of the cervix the disordered growth response to persisting estrogen concentration in inflamed squamous tissues in the presence of a nutritional deficiency? Does a thiamine deficiency act directly upon the proliferating squamous cell, impairing its enzyme pattern and its metabolism?

While the evidence presented of excess tissue estrogens, of chronic persisting infection in the cervix, and of a general deficiency of excretion of thiamine by urinary assay perhaps offers an incomplete picture to provide proof of cancer causation, the correlation of these three factors provides an interesting speculative picture. We might say that in cervical cancer the linkage between chronic infection and estrogen fixation in cervical cells explains a great deal regarding the relationship of inflammation to cancer growth. Many gynecologists have noted the great frequency of occurrence of chronic cervicitis. Probably four out of five cervices show some low-grade persisting infection in the cervix which probably remains there for years. The fixation and resultant concentration of estrogen in the cervix would tend to produce increased proliferation of the squamous cells which may be continuous over a period of years. The chronic infection has been compared to a factor producing chronic irritation in these tissues. The addition of the estrogen factor further accelerates healing or growth response as a result of this tissue-selective growth stimulant. The associated nutritional deficiency may act entirely through the liver, or its action may be purely local in the individual tissue cells, or there may be a combination. An interesting possibility is the speculation that the continuous estrogen stimulation upon the squamous cells producing chronic proliferation may result in exhaustion of these cells or of the tissue enzymes leading to an aberrant type of growth reaction. The precise relationship of the nutritional deficiency to the "wearing-out" process of the cells leading to the abnormal type of growth is not clear. Its action upon liver function and resultant estrogen accumulation is easily understood. But whether there is a direct action locally in the tissues upon cell

metabolism influencing the character of cell proliferation and growth is uncertain. But such an action seems highly probable. Thiamine is necessary for normal glycogen metabolism, and glycogen is related to estrogen activity in the cell. It has been stated that thiamine is an essential element to permit normal cell growth. It has been shown that the human carcinoma cells are low in thiamine, and the present studies have confirmed a low thiamine excretion level in a great majority of human cancer cases. This speculative action of the nutritional element would appear to be a specific influence upon growth behavior of the cell rather than a mere acceleration of cell exhaustion which one would anticipate in any growing tissue whose essential nutrition is impaired. Perhaps the exhaustion state represents an end-point in the ability of the cell to proliferate and reproduce a mature differentiated cell-product, under the environmental conditions of stress imposed by an impaired enzymic pattern. Beyond this end-point evolutionary reversion to a more primitive embryonic type of cell-offspring might occur producing the malignant cell.

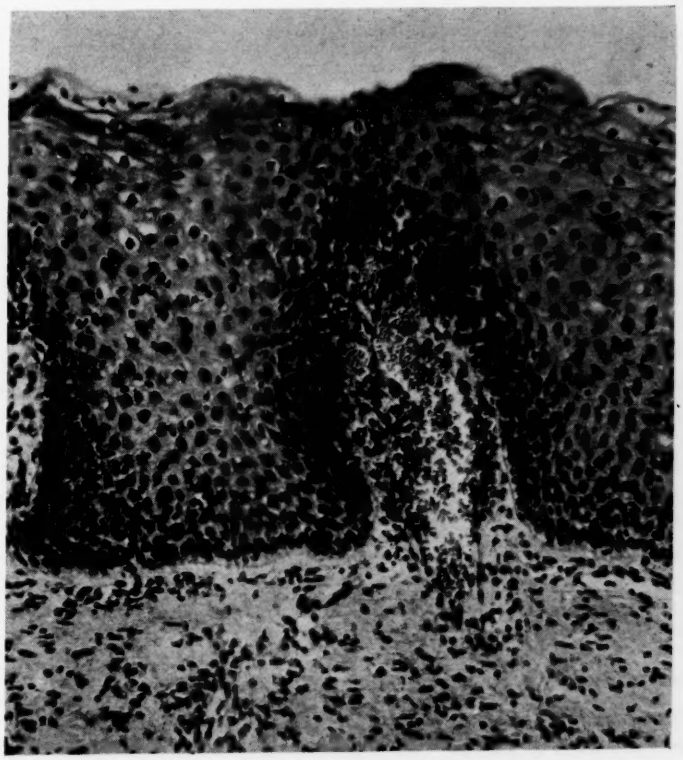

Fig. 16.—Moderately hyperactive proliferation of cervical epithelium in 31-year-old patient manifesting cervicitis, low thiamine, and high tissue estrogens.

May it not be that in all cancers there are two essential combinations of forces? First, a general body metabolic disorder characterized by a nutritional deficiency, possibly liver changes, and resultant hormonal changes. This metabolic disorder may exist with variable intensity and chronicity for years without producing cancer. Ultimately the second factor is added to the picture, namely the focalizing factor of any chronic damaging or irritating condition which provokes growth response. Whether due to infection, or inflammation, or damage, an aberrant type of growth response results, varying in character

with variations in force, intensity, and chronicity of the particular carcinogenic factors which influence that particular organ. It may be, then, that the blow to the breast which the patient recalls, is of more than coincidental significance. While it may prove harmless in the presence of a normal nutritional and hormonal balance, in the presence of the abnormal metabolic status, the resultant healing growth-reaction may result in growth of a malignant character.

Comment

During the course of this study we have been impressed by the consistent finding of a different cell morphology at the squamocolumnar junction, both in cytology smears and in tissue biopsies, in cases exhibiting the infection-estrogen-nutrition combination. This unusual cell-change has been most impressive in the group of microscopic preinvasive cancers, where no demonstrable clinical growth was detectable. Yet the cell-change was definite in cytology and was consistently confirmed by biopsies (e.g., Figs. 16 and 17).

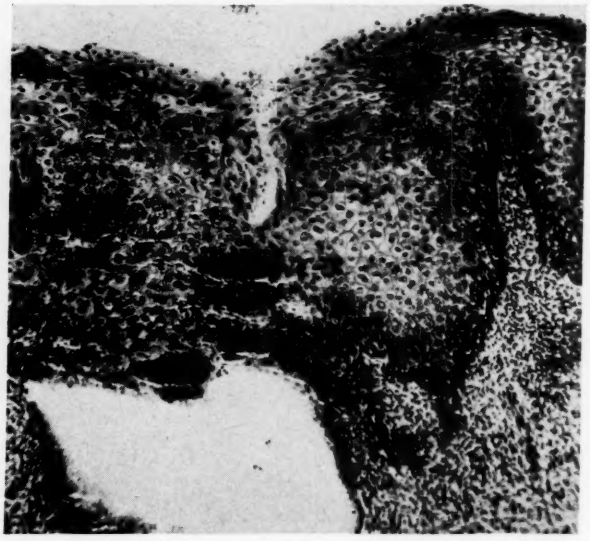

Fig. 17.—Extremely hyperactive proliferation in cervical epithelium in 28-year-old manifesting cervicitis, low thiamine and high tissue estrogens. Note marked nuclear changes in squamocolumnar zone.

We feel sure that cytology techniques offer us a valuable means of early cancer diagnosis. But more significantly they also provide us with new microscopic sights to probe into the hidden recesses which have long held the secret of the fundamental nature of cancer growth.

Summary

1. Cytology studies have been found valuable in early diagnosis of cervical cancer, and in estimating endogenous estrogen.

2. Comparative vaginal and cervical cornification counts have revealed greater concentration of estrogens in the cervix in 87 per cent of cases studied.

3. Some degree of chronic cervicitis is believed to be present in four of five adult cervices.

4. Estrogen-fixation and concentration in infected cervical tissues is believed to be a growth-stimulating factor predisposing to cancer.

5. Evidence of excessive tissue estrogen has been found in 92 per cent of 50 cervical cancers.

6. Deficient urinary thiamine excretion has been found in 86 per cent of 50 cervical cancers. Ten per cent of 50 controls showed the same deficiency.

7. Riboflavin deficiency was found in 38.8 per cent of cancer cases, and in 6.8 per cent of the controls.

8. Studies of cervical biopsies illustrating abnormal growth proliferation in the presence of cervicitis, excess tissue estrogens, and low thiamine excretion are presented.

9. Partly by speculation, partly by interpretation of evidence presented, an attempt is made to correlate infection, excessive tissue estrogens, and nutritional deficiency in the production of cervical carcinoma of the squamous type.

10. The possible concentration of estrogen around cervical cancer lesions arouses great hope for improved therapy with radioactive isotopes. Just as thyroid cancer may succumb to radioactivated iodine, so also may the selective affinity of estrogen for proliferating Müllerian tissues enable successful treatment of cancer of the cervix.

Dr. W. A. G. Bauld, Director of the Gynecologic Cancer Clinic, has closely collaborated throughout, and by his keen interest, ready counsel, and constructive criticism has contributed immeasurably to the successful completion of the present stage of this work. Appreciation is also expressed to Drs. J. R. Fraser, N. W. Philpott, and J. S. L. Browne for valuable advice and cooperation in the preparation of this work: to the Nutrition Department of the Medical Laboratories of the McGill University Clinic, and to Dr. P. J. Kearns, Chief of the Gynecologic Pathology Laboratory of the Royal Victoria Hospital: and to Drs. W. A. Andreae and M. M. Hoffman for their assistance and advice regarding nutritional studies and liver function tests, respectively.

Grateful thanks is also tendered to Dean Meakins, Director of the Medical Laboratories of the McGill University Clinic. Assistance in this work has also been rendered by Dr. Paul Chevalier, Molson Fellow in Cancer Research, and Miss Evelyn Dakin, Director of Technicians in the Gyne-cytology Laboratory, who, through her tireless efforts and technical genius, has made a major contribution to this work. Mrs. Dorothy Peden of the Gynecologic Pathology Department has rendered valuable help in preparing pathologic sections. Miss Janet Alexander has done excellent work in the biochemical studies of the thiamine and riboflavin levels.

Photomicrography by H. S. Haydon, F.R.P.S., and H. Coletta.

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THE EFFECT OF BODY POSTURE ON UTERINE POSITION

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FORTY-FIVE years ago Tandler[1] taught that the normal uterus is a movable organ. In 1936, Harris, Mengert, and Plass[2] demonstrated with bimanual palpation that it alters its position in response to postural change. Diddle, Mengert, and Earl[3] confirmed this finding radiographically in 1939 with an exhibit of superimposed photographs and roentgenograms. Part of this material was utilized in the present study to illustrate the amount of uterine movement with change in body posture. Diagrammatic line drawings were used, since it was impossible from a practical standpoint to reproduce the original material.

Subjects

Data of four representative subjects were selected from the thirteen gynecologic patients forming the basis of the exhibit by Diddle, Mengert, and Earl.[3] Two of these four subjects were normal, apparently healthy, young women admitted for various minor complaints not stemming from the pelvis. They were selected because one of them presented typically average genitalia, while the freely movable uterus of the other habitually lay in mild flexioretroversion. Two were postmenopausal, and were admitted for repair of an incomplete and a complete uterine prolapse, respectively. All four women were in excellent nutritional states.

Method

The length and direction of the uterine canal were visualized by means of a ureteral catheter, inserted to the fundus, and cut off flush with the external cervical os. The surface of the vaginal portion of the cervix was visualized with a snugly fitting, aluminum contraceptive cap. The total weight of both of these artifacts was small, less than 13 Gm., and is believed to exert no significant influence on the final result. In addition, the urinary bladder was delineated in two subjects (normal anteversion and complete uterine prolapse) by the instillation of sodium iodide solution. Metal markers were placed on the medial and lateral aspects of the right thigh and, in some instances, above the right iliac crest.

Anteroposterior roentgenograms of each subject lying supine were made. Following this she turned to the right side for the lateral recumbent view. Next, anteroposterior, and right lateral roentgenograms were made with each subject successively sitting and standing. The subject remained in a given position for fifteen minutes preceding exposure of each film to allow for visceral accommodation and adjustment, possibly an unnecessary precaution. Photographs of the nude subject in the several positions were made from a standard distance.

All possible landmarks were utilized to facilitate superimposition of photograph and roentgenogram. Actually, they could not be matched exactly because of dispersion of roentgen rays. In other words, it is impossible to superimpose two pictures when one is made with parallel light rays and the other with roentgen rays diverging at angles approaching 35 degrees. Many methods, including the metal markers mentioned above, were tried and discarded. The best possible correlation of roentgenogram and photograph was achieved by trial and error, after careful study of all discernible landmarks. Three observers in joint session, including Mr. Fred Kent, official photographer of the University of Iowa, carefully matched each pair of pictures. The resulting product was legible by transmitted light, but unsuited for reproduction on the printed page. Therefore, the accompanying diagrams were carefully drawn from the roentgenograms and photographs and faithfully adhere to the original. In each instance red lines indicate the supine, or the lateral recumbent position, as the case may be. Solid black lines represent the sitting position. Standing is portrayed by dotted lines.

For purposes of this study, four variations of uterine position are recognized, viz: station, flexion, version, and cession. "Station" is employed to indicate the height of the cervix in the pelvic basin. "Flexion" refers to bending of the uterine canal. "Version" means rotation of the entire uterus around a transverse axis. The amount of "cession" indicates the distance of the cervix from the symphysis pubis. Thus, a "retrocessed" uterus sags posteriorly toward the sacrum.

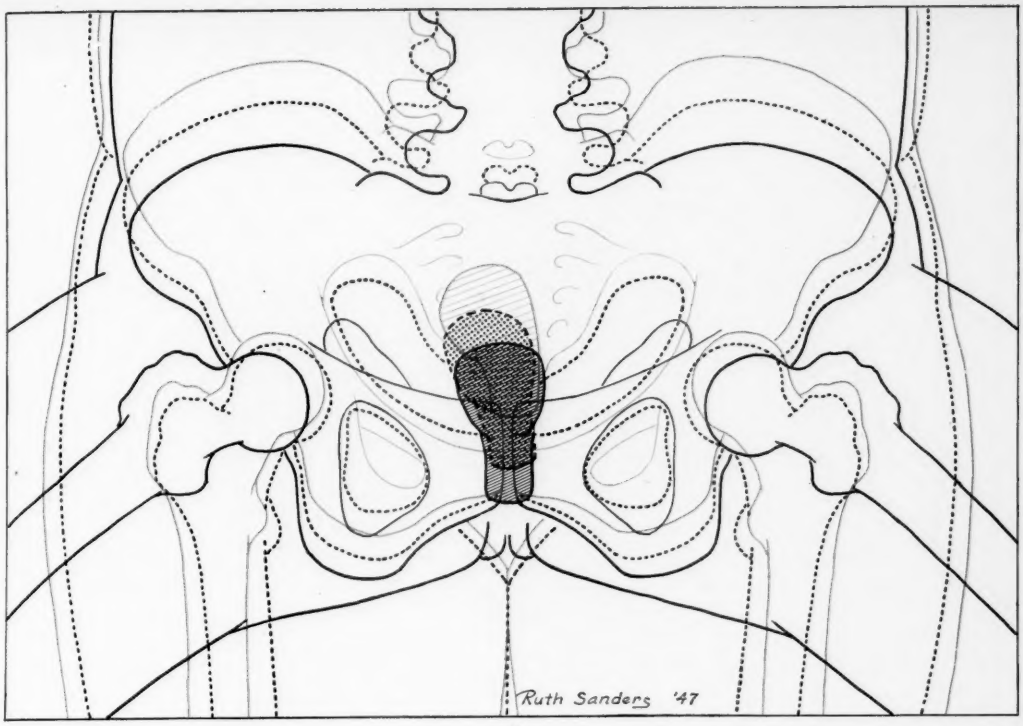
Results

The original study, presented as an exhibit and referred to above, included thirteen patients of whom ten were normal from a gynecologic standpoint, and three suffered with genital prolapse. Since results were quite uniform in these women, irrespective of parity, it is superfluous to diagram the findings of each. Therefore, only average results illustrated by a normal subject with habitual anteversion (Fig. 1), a normal subject with habitual flexioretroversion (Fig. 2), and the findings from a patient with incomplete (Fig. 3), and a patient with complete prolapse (Fig. 4) are presented.

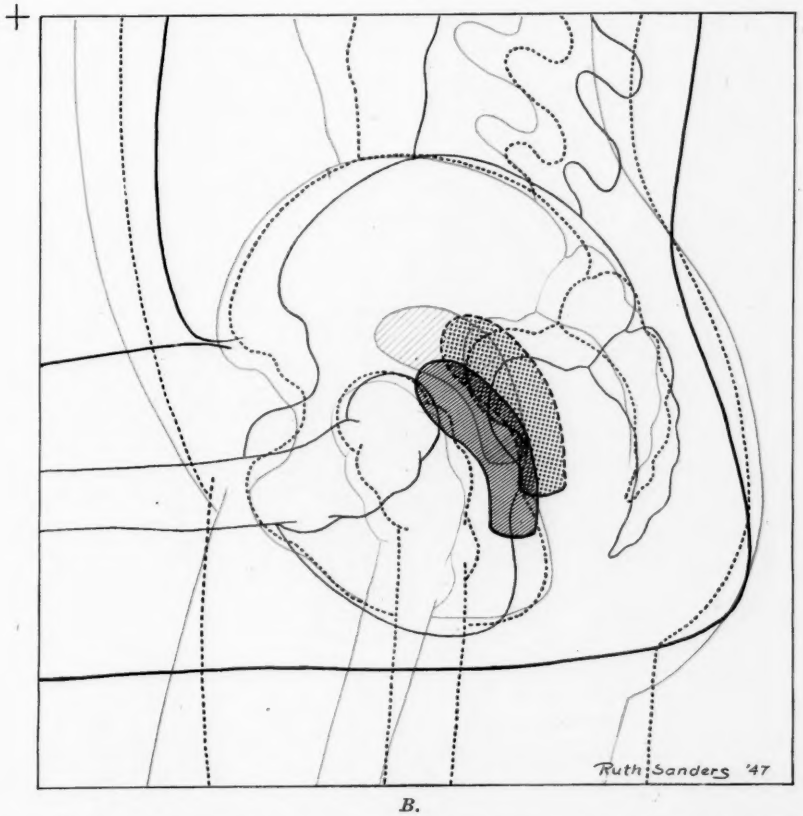
Habitual Anteversion.—Figs. 1*A* and 1*B* represent characteristic positions of the uterus in a subject with normal genitalia and habitual anteversion. The results portrayed here are typical, irrespective of parity, of other women of the original study. As might be expected, lowest uterine stations accompanied vertical positions of the trunk (Fig. 1*A* and 1*B*). There was no significant alteration of uterine flexion or version with change of body posture. On the other hand, retrocession was perceptible in the standing posture, and markedly increased with sitting.

Habitual Flexioretroversion.—Figs. 2*A* and 2*B* represent characteristic positions of the uterus in a subject with normal genitalia and habitual flexioretroversion. The results portrayed here are typical, irrespective of parity, of other women of the original study. In conformity to the previously described subject, the lowest stations accompanied vertical positions of the trunk. There was little change in flexion and version between the lateral recumbent and standing postures. On the other hand, a considerable increase in retroflexion and retroversion was noticed when the subject sat upright. The amount of retrocession in the two erect attitudes (sitting, standing) was similar, but much greater than with right lateral recumbency.

Incomplete Prolapse with cystocele.—Figs. 3*A* and 3*B* demonstrate uteropelvic relationships in a postmenopausal woman with incomplete prolapse and moderate cystocele. Flexion did not occur with any position. Interestingly,



A.

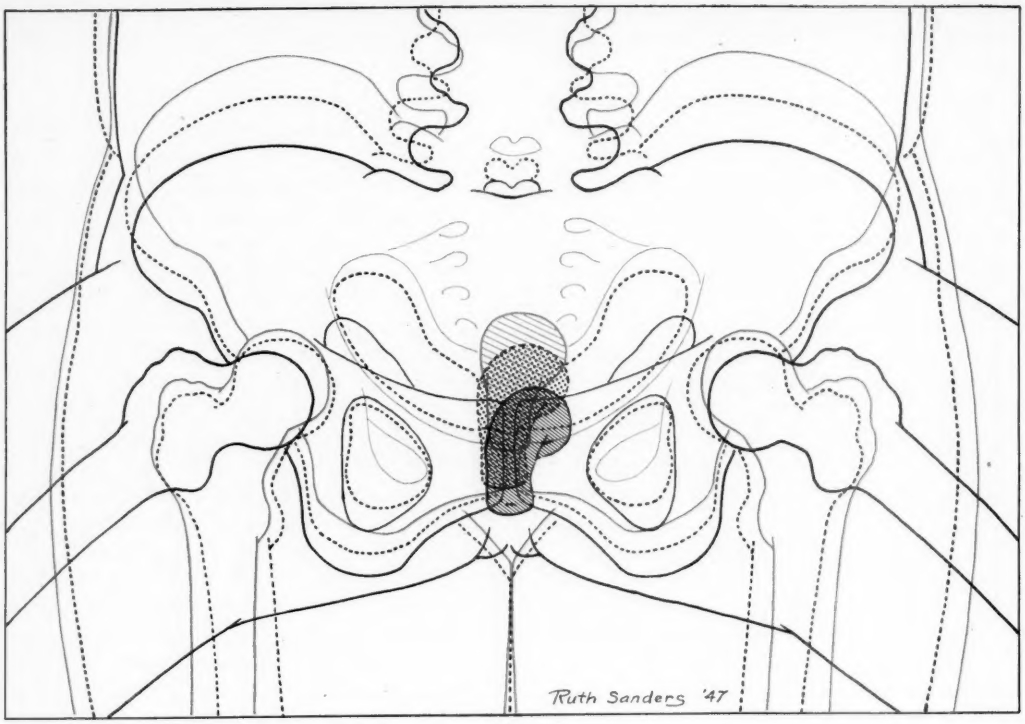


B.

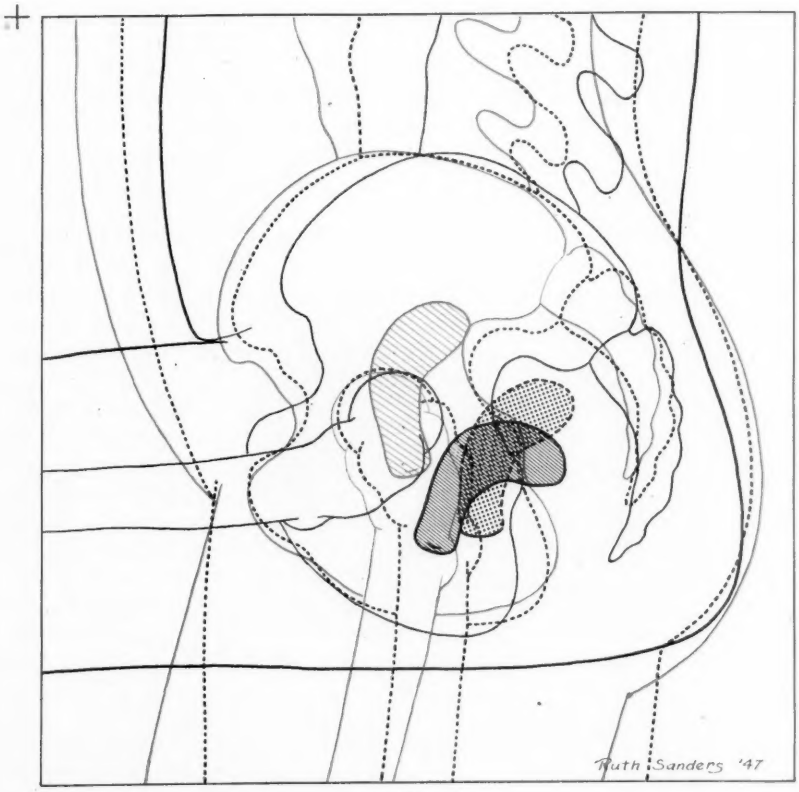
Fig. 1.—Habitual anteversion. Red lines indicate conditions when supine; solid black lines, sitting; dotted lines, standing. This sequence is observed in Figs. 1, 2, 3, and 4.

Fig. 1*A*.—Note lowest uterine stations accompanied vertical positions of the trunk.

Fig. 1*B*.—Descent of the uterus is also evident in this view. Note definite retrocession in the sitting posture.



A.

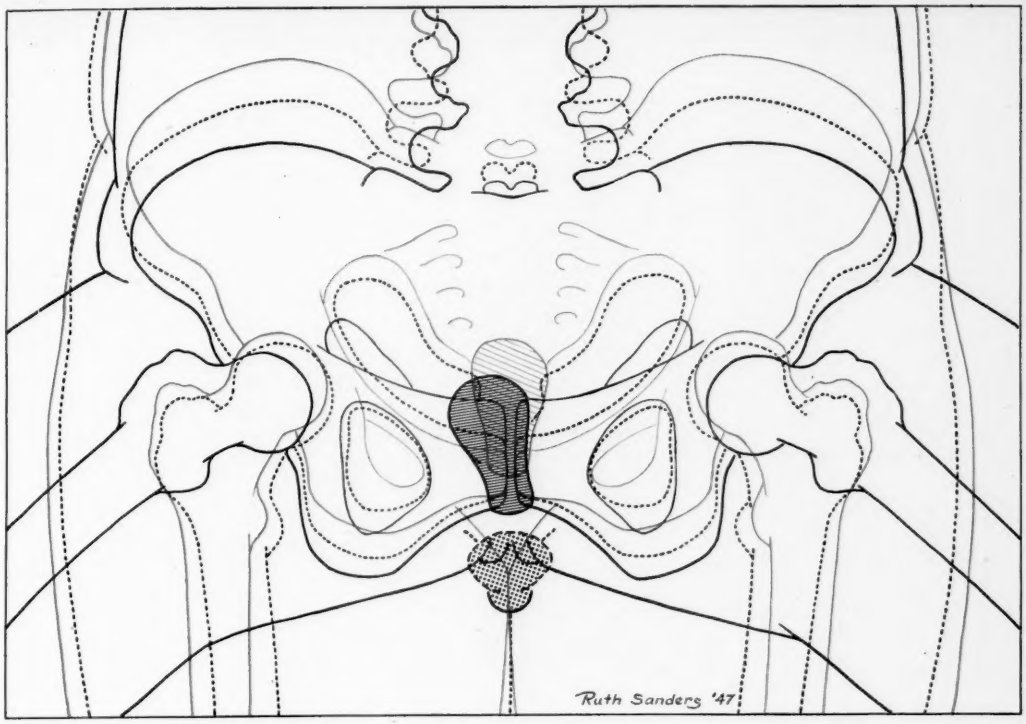


B.

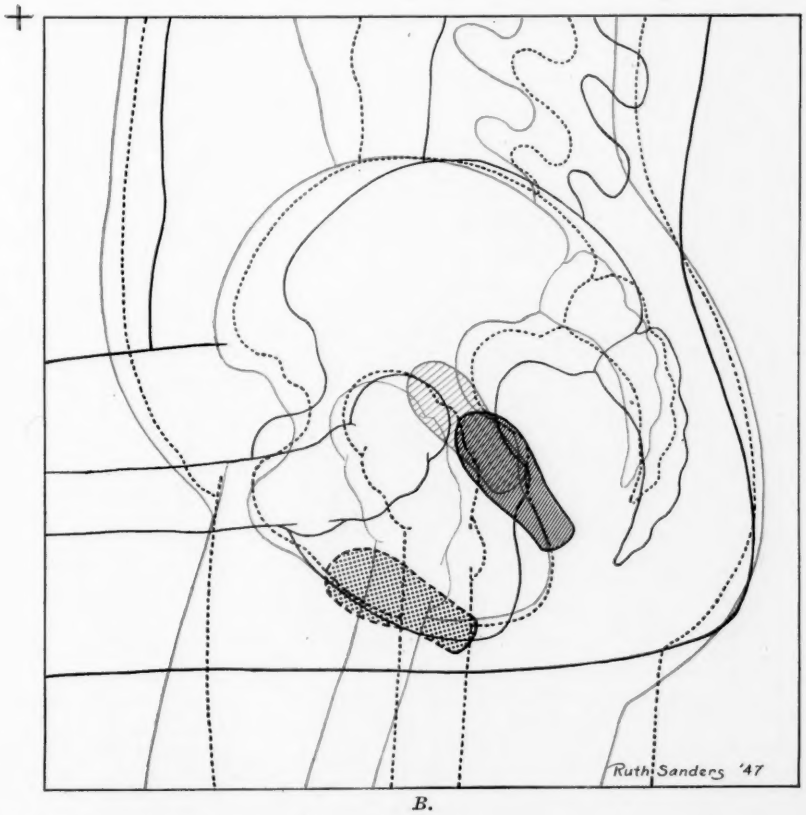
Fig. 2.—Habitual flexioretroversion.

Fig. 2*A*.—Note slight, descending station of the uterus. The uterus reached its lowest station with the patient sitting.

Fig. 2*B*.—Retroflexion and retroversion were noticeably increased in the sitting posture. Retrocession was increased with both erect attitudes (sitting, standing).



A.

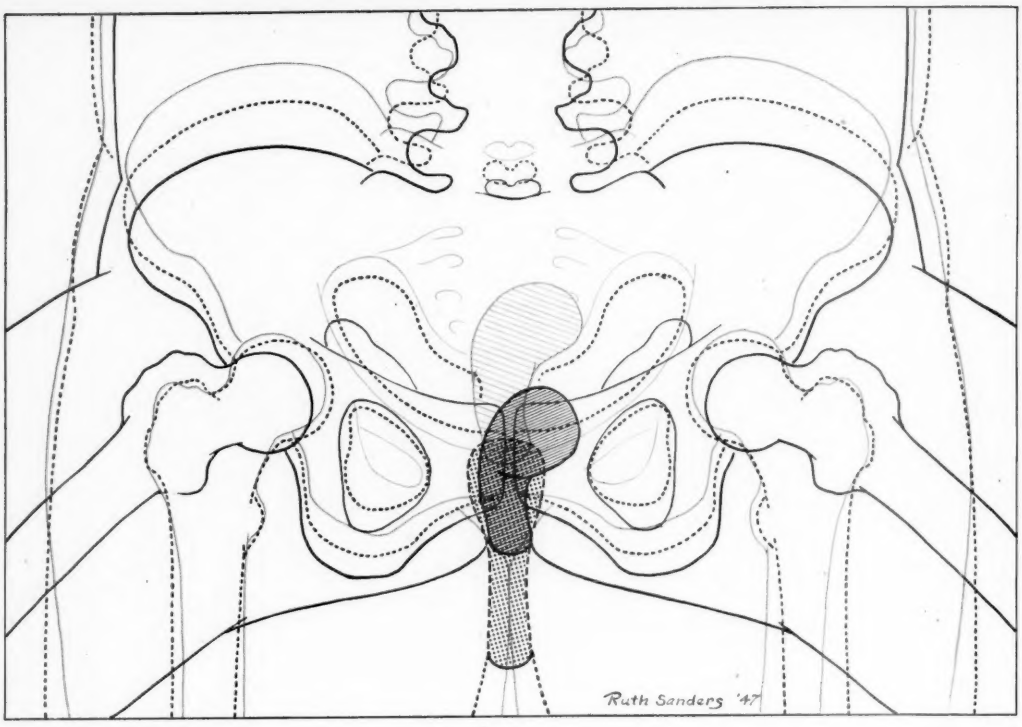


B.

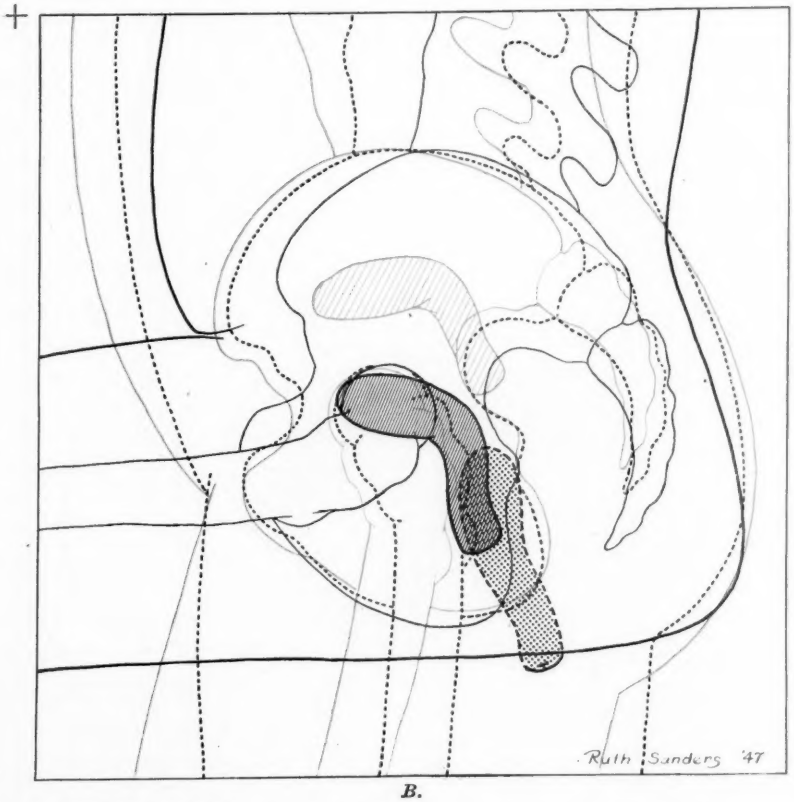
Fig. 3.—Incomplete prolapse with cystocele.

Fig. 3*A*.—Note descent of the uterus as the patient became progressively erect.

Fig. 3*B*.—Note increased anteversion with marked forward displacement of the entire uterus (*ante*cession) in the standing position. Also note the uterine canal was nearly horizontal. These findings are direct negation of the common teaching that *retro*version is a necessary prelude to prolapse.



A.

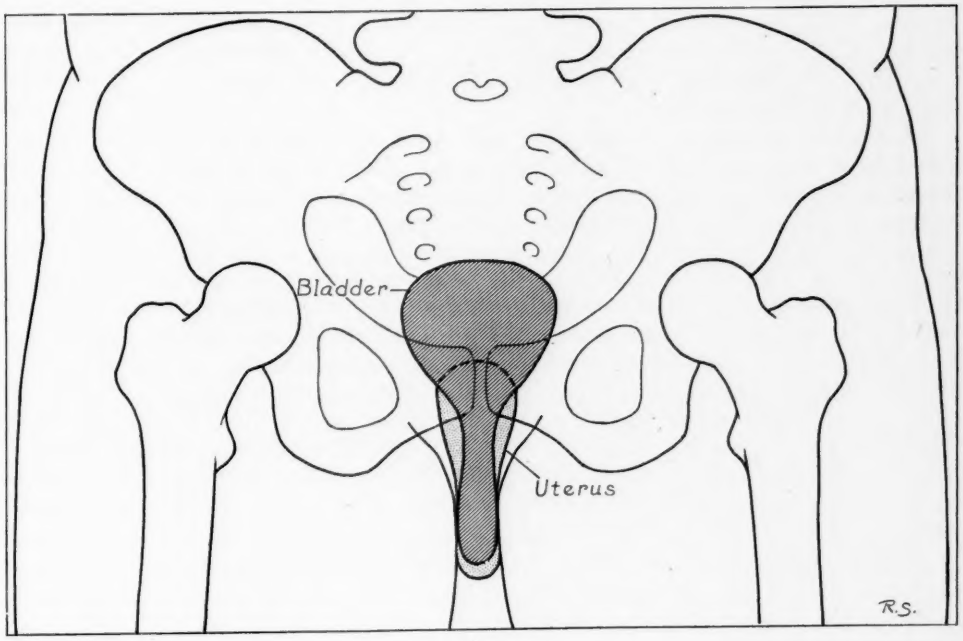


B.

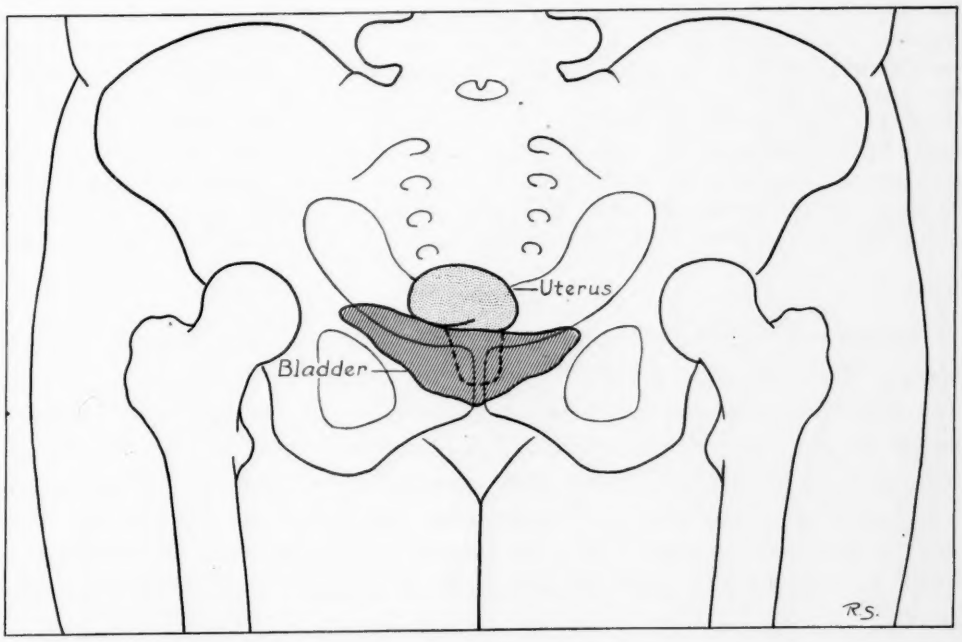
Fig. 4.—Complete prolapse.

Fig. 4*A*.—Note apparent elongation of cervix as the uterus descended. (Complete prolapse did not happen to occur during the course of the study.)

Fig. 4*B*.—Note elongation of cervix and straightening of the uterine canal with descent.



A.



B.

Fig. 5.—Urinary bladder relationships. Only one posture, standing, is depicted here. Therefore, the linear system pertaining to Figs. 1, 2, 3, and 4 is not applicable. Solid, slanting lines represent the urinary bladder. Dotted lines indicate the uterus.

Fig. 5*A*.—Visualized urinary bladder of patient with complete prolapse (Fig. 4). Note position of the uterus in relation to the floor and dome of the bladder, with its dependent sac preventing complete emptying.

Fig. 5*B*.—Visualized urinary bladder of patient with habitual anteversion (Fig. 1) inserted for comparison.

version was *forward,* and was especially marked in the standing posture. Coincident *with increased anteversion* in standing, the *entire uterus descended,* and lay at the vulval orifice with the axis practically horizontal. This finding is a direct negation of the common teaching that *retro*version is a necessary prelude to uterine prolapse.

Complete Prolapse.—Figs. 4*A* and 4*B* illustrate conditions in a postmenopausal woman with complete prolapse, defined as descent of the entire uterus outside the carunculae myrtiformis. Such conditions were found in this patient at the times of admission and operation, but not during the course of this study. A few days' bed rest frequently permits an amazing amount of recovery of the supportive powers of the fascia propria. On the other hand, the full extent of the prolapse promptly recurs after resumption of the erect posture. Uterine station was essentially normal with the patient supine and, as might be expected, the lowest station accompanied the standing position. Flexion, most marked with the patient lying on her right side, diminished when she sat and disappeared when she stood erect. This is perfect correspondence to the classic teaching that the anteflexed uterus cannot prolapse. It is of interest that straightening of the uterine canal accounts for its apparent lengthening in the anteroposterior view (Fig. 4*A*). Version and cession were not significantly altered by change of posture.

The Urinary Bladder.—Figs. 5*A* and 5*B* show the relationship of the urinary bladder to the prolapsed (Fig. 5*A*) and the normally placed (Fig. 5*B*) uterus. The subjects of Figs. 4 and 1, respectively, were used for this demonstration. As mentioned earlier, the urinary bladder was rendered opaque to the roentgen ray and is illustrated by solid, slanting lines. The uterus is delineated by dotted shading. The bladder assumed a gourdlike shape in the patient with prolapse (Fig. 5*A*), and its floor descended outside the body with the cervix. Moreover, the bulk of the urinary bladder occupied a station above that of the uterine fundus. In other words, the uterus lay posterior, instead of superior, to the urinary bladder. Obviously the saclike, dependent portion of the bladder cannot be emptied completely, and accounts for the residual urine commonly seen with this condition. Fig. 5*B* of the normally placed urinary bladder of the subject of Fig. 1 is inserted for comparison.

Discussion

Objectivity is the chief value of the present study. Movement of the uterus, with the canal artificially rendered opaque by lightweight materials, was seen and measured on roentgenograms. Harris, Mengert, and Plass reported uterine movement from ante- to retroversion with change of body posture of women confined to bed with pulmonary tuberculosis but their study was based upon the subjective interpretation of bimanual palpation. Gross change only was reported and they found that version from anterior to posterior uterine position (or vice versa) did not occur in less than twenty-four hours.

Passage of time is important in any consideration of uterine mobility, since intestines must be displaced before *profound* change is possible. Moreover, uterine weight, effective for intestinal displacement, is small in relation to that of viscera displaced. Therefore, the rate of change is slow and depends to some degree upon intestinal peristalsis. On the other hand, minor degrees of change can occur during the passage of minutes, without the necessity for in-

testinal displacement. It is entirely probable that the gross changes reported by Harris, Mengert, and Plass require hours because of the necessity of intestinal displacement. The minor changes demonstrated by the present study may be effected immediately because intestines are locally compressed and not displaced.

It is commonly taught that the anteverted uterus cannot prolapse. In other words, the uterus must assume midposition or become retroverted before descent begins. This was not the case in the patient with incomplete prolapse, since descent occurred with the uterus anteverted, and the canal practically horizontal as she stood erect. Moreover, complete prolapse of the anteverted uterus following the Watkins-Wertheim interposition operation does occur. Such a patient was observed by the authors.

It is apparent that maintenance of uterine station and cession depends upon integrity of fascial support. In contradistinction, the uterine body bends (flexion) and turns (version) on a transverse axis as a result of the combined influences of its muscular tone, position of the intestines, body posture, and perhaps the tilt of the pelvis. It was clearly demonstrated that the normal uterus tended to gravitate in conformity to the several positions assumed by the subject. This tendency was distinctly evident in the normal, and greatly exaggerated in patients with uterine prolapse.

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STUDIES IN RH-ISOIMMUNIZATION IN PREGNANCY

Observations in a Series of Ninety-Six Sensitized Women

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CONTRIBUTIONS to medical literature relating to the Rh factor have reached an impressive total since the discovery of this erythrocytic antigen by Landsteiner and Wiener.[1] As a result of these studies many fundamental facts concerning the clinical, genetic, immunologic, anthropologic, and pathologic aspects of the subject have been elucidated. Students in this field, however, continue to be aware of the existence of many unsolved problems. A striking lack has been the application, in a comprehensive manner, of this mass of knowledge to large groups of pregnant women and their offspring. Data accumulated from such material would serve not only to lend numerical support to preexisting ideas, but would also tend to clarify certain still-nebulous facets of the subject. It is the purpose of this paper to deal with observations made on a group of 12,275 patients studied during the period August 1, 1945, to August 31, 1946. Of the total, 96 isoimmunized women were encountered. Particular reference will be made in the latter group to a correlative study of quantitative prepartum antibody titer with neonatal mortality.

Even as late as 1945 Rh studies were, in general, being done in a sporadic fashion. The birth of an obviously erythroblastotic infant or an obstetric history suggestive of this complication were the usual indications for serologic studies. In an effort to correct this situation in the community, the Obstetrical and Gynecological section of the Baltimore City Medical Society in August, 1945, sponsored the establishment of a central laboratory, the purpose of which was to make readily available to every physician facilities for Rh studies on all expectant mothers. The organization and method of operation of this laboratory have been fully described in a previous publication.[2] Owing to the splendid cooperation of physicians and patients, it has been possible to make systematic studies in the large group of patients referred to above.

In succeeding pages the following topics will be discussed:

I. Distribution and Incidence of Rh Types.
II. Distribution and Incidence of Rh-Isoimmunization.
III. Incidence of Erythroblastosis Fetalis.
IV. Nature and Specificity of Antibodies.
V. Correlation of Prepartum Antibody Titer With Neonatal Mortality.
VI. The Course of Isoimmunization During Pregnancy and in the Puerperium.
VII. Postpartum Persistence of Antibodies.
VIII. Correlation of Parity With Initial Evidence of Rh-Isoimmunization.

Materials and Methods

On all patients referred for study a complete obstetric and transfusion history is obtained. Samples of blood procured by venipuncture are first grouped by Landsteiner's technique.[3] The Rh type is determined by the Landsteiner-Wiener[4] procedure using a suitable dilution of a potent anti-Rh_0 serum of human origin prepared in this laboratory. All definitely positive reactors are thus screened out. No further study is made of these patients unless a previous history of erythroblastosis fetalis is present. In the latter instance Rh′, Rh″, Hr and M-N studies are carried out on the patient and her immediate family. All doubtful and negative reactions are checked, using two additional potent anti-Rh_0 sera of human origin obtained from other sources. It is obvious that even with such checking the relatively small proportion (about 1.5 per cent) of positive individuals of types Rh′, Rh″, and Rh′R″ will be classified as Rh negative. For all practical purposes such individuals should be classified as Rh negative in regard to isoimmunization by pregnancy or multiple transfusions. In the event that sensitization is detected, negative individuals are further tested with anti-Rh′ and anti-Rh″ sera of human origin.*

The detection of Rh-isoimmunization is accomplished by the use of the conglutination test of Wiener.[5] Further comments concerning certain aspects of this test are made in section V. The so-called "blocking" test[6] is utilized to afford additional confirmatory evidence of sensitization. This procedure occasionally has been found to offer some technical interpretive difficulties; moreover, it does not lend itself as readily to quantitation as does the conglutination procedure. The Diamond slide test[7] is occasionally used for a similar purpose. This technique has not been found adaptable to testing on a large scale and, moreover, leads to interpretive difficulties at times due to excessive rouleaux formation and rapid drying of the preparation.

Quantitative estimation of antibodies is carried out by parallel conglutination and agglutination tests upon all sera demonstrating the presence of immune bodies. For this purpose, 2 per cent suspensions of pooled O Rh-positive cells in pooled compatible plasma, serum, and normal saline solution, respectively, are used. More recently, bovine albumin solution as recommended by Diamond and Denton[8] has been used as the suspending vehicle for the Rh-positive test cells. Parallel studies utilizing a variety of vehicles are being carried on at present. Preliminary studies appear to indicate a greater sensitivity of the procedure utilizing bovine albumin solution. The urgent need for further standardization of the conglutination test is commented upon in a subsequent section of this paper. The conglutination test is controlled by the use of O Rh-negative cell suspensions. In this manner occasional instances of maternal isoimmunization not attributable to the Rh factor may be detected.

The nature of antibodies present in a particular case is determined from the results of the agglutination and conglutination tests. When both procedures give equal titers only bivalent (agglutinins) antibodies are assumed to be present.[9] A positive reaction with the conglutination test alone is presumed to indicate the presence of only univalent (glutinins) antibodies. Positive reactions of varying titer obtained with both procedures have been taken to indicate the presence of both types of antibodies, when there exists a relative excess of one type. Specificity of antibodies is determined by study of serum reactions with cells of known type including Rh_0, Rh′, and Rh″, M and N.

Blood group studies are made of the husbands of all Rh-negative women, and whenever sensitization exists, similar study is made of all living children. Hr

*Sera obtained from the laboratory of Dr. A. S. Wiener.

studies are done on all Rh_1 positive husbands of sensitized women.[10] In many instances the husband's parents are studied in a further effort to determine homo- and heterozygosity.

Whenever possible it has been our policy to study Rh negative patients at monthly intervals up to the eighth month of pregnancy and then at biweekly intervals to term. A sample of cord blood is obtained from the baby at the time of delivery for Rh typing and detection of adsorbed antibodies. Samples of maternal blood are studied on the tenth day and at six weeks post partum. In a limited number of sensitized patients bimonthly serum studies are being made during the first postpartum year to determine the rate of disappearance of antibodies. In all instances where erythroblastosis fetalis occurs in the infant, abstracts of the hospital chart including clinical notes, laboratory data, and pathologic studies become a part of the record.

During the thirteen-month period covered by this study it has been necessary at intervals to alter the protocol because of more recent developments. Although all serologic studies were performed in this laboratory, it should be noted that clinical and pathologic data were assembled from a number of sources. As a result the data in some instances were not as complete as would have been desirable. More recently an effort has been made to establish a uniform procedure for the study of all Rh-negative women and their offspring.

I. Distribution and Incidence of Rh Types

A total of 12,275 women were typed in this laboratory during the thirteen-month period covered by the study. Of this group, 12,140 were unselected individuals whose bloods were examined as a routine of prenatal care. The remaining 135 represent a group referred, because of known Rh negativity, for detailed serum studies. The ratios of positive and negative, white and Negro females conform closely to previously established figures[1, 4, 11] (Table I). The relative scarcity and expense of sera of anti-Rh′ and anti-Rh″ specificity permitted only limited use of these reagents. More recently, all Rh-negative women, their husbands, children, and living grandparents have been studied with all available Rh sera. The continuing availability of large numbers of patients for serologic studies affords opportunity for future genetic and anthropologic investigations.

TABLE I. DISTRIBUTION AND INCIDENCE OF RH TYPES IN TOTAL FEMALE GROUP*

TOTAL FEMALE PATIENTS	RH POSITIVE		PER CENT RH POSITIVE		RH NEGATIVE		PER CENT RH NEGATIVE	
	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO
12,140	7,700	2,800	84.4%	92.7%	1,420	220	15.6%	7.3%

*This is an unselected group and does not include 135 additional known Rh-negative women who were referred here for serum studies.

II. Distribution and Incidence of Rh-Isoimmunization

It has been estimated statistically that in the general population 41 per cent are homozygous or RhRh; 46 per cent are heterozygous, or Rhrh; and 13 per cent are negative, or rhrh. Thus, 11.3 per cent of all matings occur between Rh-negative females and Rh positive-males. As 5.33 per cent (13 per cent of 41 per cent) will be with homozygous men, and 5.98 per cent (13 per cent of 46 per cent) will be with heterozygous men, 5.33 per cent plus one-half of 5.98 per cent, or 8.32 per cent, of all children born will be Rh-positive children of Rh-negative mothers.[12] Theoretically, therefore, opportunity for maternal isoimmunization exists in 8.32 per cent (1 in 12) of all births. However, the observed incidence is somewhat less than one-tenth of the theoretical figure.

In our group of 12,275 pregnant women, 0.77 per cent, or 1 in 128 deliveries occurred in a sensitized woman. That this does not correspond with the actual incidence of erythroblastosis fetalis is noted and discussed in a subsequent section. Of the total, 1,775 were Rh negative. One hundred forty of these women had Rh-negative husbands. Eighty-six Rh-negative sensitized women were encountered in the period comprising this study. In terms of the total negative group, therefore, the incidence of isoimmunization was 4.84 per cent. If the Rh-negative women with Rh-negative husbands are excluded, the incidence of isoimmunization rises to 5.26 per cent.

Among the 1,635 Rh-negative women with Rh-positive husbands, 727 were primigravidas, and 908 multigravidas. There were nine sensitized Rh-negative primigravidas, or an incidence of 1.24 per cent; and 77 multigravidas, an incidence of 8.48 per cent. An almost eightfold incidence of isoimmunization was thus observed in the latter group as compared with the former.

The discrepancy between theoretical potentiality for isoimmunization and its actual occurrence can be attributed to: (1) the relatively infrequent appearance in primigravidas as shown above, and (2) individual variations in placental permeability, antigenic strength, and response to antigenic stimulation.

It is of interest to note that ten instances of Rh-isoimmunization occurred in the group of 10,500 Rh-positive women (Table II). Nine of these occurred in women who belonged to subtypes Rh′ or Rh″. Since these groups theoretically constitute about 1.5 per cent of the total positive group, the incidence of isoimmunization, 5.7 per cent, roughly approximates that observed in the pure negative group. These observations serve to emphasize the statement previously made, i.e., that to all intents and purposes such individuals behave as if they were Rh negative. One instance of isoimmunization was observed in an Rh_1 individual. This patient who was Hr negative, developed anti-Hr immune bodies of a degree sufficient to produce typical erythroblastosis in her second child. Further related details of the case are to be presented in a future report. It is worthy of note that the expected theoretical incidence of Hr negativity in the Rh-positive group was about 20 per cent, or 2,100 women. The occurrence of only one case of isoimmunization is an index of the weak antigenicity of the Hr factor.[13]

TABLE II. DISTRIBUTION AND INCIDENCE OF RH-ISOIMMUNIZATION IN TOTAL FEMALE GROUP

TOTAL RH-POSITIVE WOMEN	TOTAL RH-POSITIVE SENSITIZED WOMEN	PER CENT OF RH-POSITIVE SENSITIZED WOMEN	TOTAL RH-NEGATIVE WOMEN*	TOTAL RH-NEGATIVE SENSITIZED WOMEN	PER CENT OF RH-NEGATIVE SENSITIZED WOMEN
10,500	10	.095%	1,775	86	4.84%

*One hundred forty Rh-negative women of this group had Rh-negative husbands. See Text.

III. Incidence of Erythroblastosis Fetalis

Of the total of 96 women included in this study, the outcome of pregnancy is known in 79 instances. The remaining group of 17 patients include seven who are still pregnant at the time of preparation of this report, and hence the outcome of whose pregnancy is not known now, and 10 who were either not available for serial studies or who aborted early in pregnancy.

Fifty-three, or 67.1 per cent, of the 79 patients referred to above gave birth to infants with varying manifestations of erythroblastosis fetalis.* A surpris-

*The term erythroblastosis fetalis is used in a generic sense to designate all evidences of fetal or neonatal hemolytic disease resulting from erythrocytic antigenic incompatibility between mother and fetus. Clinical manifestations include anemia, erythroblastemia of significant degree, icterus, hepato- and splenomegaly, hydrops, etc.

ingly large group, 26, or 32.9 per cent, gave birth to offspring who displayed no evidence of congenital hemolytic disease (Table III). *This fact, namely, that isoimmunization is not necessarily synonymous with the occurrence of disease in the newborn infant, is worthy of stress.* It has been noted previously[14-16] in a relatively small number of patients.

TABLE III. INCIDENCE OF ERYTHROBLASTOSIS FETALIS IN THE OFFSPRING OF SEVENTY-NINE SENSITIZED WOMEN

	NUMBER OF INFANTS	PERCENTAGE OF TOTAL
Evidence of erythroblastosis fetalis	53	67.1%
No evidence of erythroblastosis fetalis	26	32.9%
Total	79	100.0%

On the basis of a 67 per cent incidence of erythroblastosis fetalis in 79 patients, approximately four of the seven undelivered patients would be expected to give birth to infants with stigmas of this disease. Thus, in 12,275 deliveries, congenital hemolytic disease occurred 57 times, or once in 215 deliveries for an incidence of 0.46 per cent. In regard to the Rh-negative group (1,775 patients) the incidence of erythroblastosis fetalis was 3.21 per cent. This is significantly less than the 4.84 per cent incidence of isoimmunization noted above. Review of our material indicates that the difference is due (1) to failure of maternal antibody titer to reach a degree sufficient to produce disease in the infant. or (2) delivery of an Rh-negative infant in a mother whose antibodies were formed as a result of some previous stimulation.

IV. Nature and Specificity of Antibodies

There is general agreement that antibodies of Rh_0 specificity are those most commonly encountered in cases of Rh-isoimmunization. The ubiquity of the Rh_0 antigen[17] occurring as it does in about 85 per cent of all Rh-positive Caucasians accounts in part for this predominance. The greater antigenic potency of the Rh_0 factor[18] is likewise of importance. Thirty-two of 38 sensitized patients in our series in whom antibody specificity was determined displayed immune bodies of the anti-Rh_0 type (Table IV). Four had Rh_1 antibodies; one, anti-Rh_2; and one, anti-Hr_1 immune bodies. Antibodies of pure Rh′ and Rh″ specificity were not encountered. These occur uncommonly and when present are often not in pure form. Thus, sera apparently of anti-Rh′ or anti-Rh″ specificity have frequently been found to be mixtures of univalent anti-Rh_0 immune bodies and Rh′ or Rh″ agglutinins.[19]

TABLE IV. ANTIBODY SPECIFICITY IN THIRTY-EIGHT ISOIMMUNIZED WOMEN

SPECIFICITY	NUMBER OF CASES	PERCENTAGE
Anti-Rh_0	32	84.2%
Anti-Rh_1	4	10.5%
Anti-Rh_2	1	2.6%
Anti-Hr_1	1	2.6%
Total	38	99.9%

In our series of cases there were no instances of erythroblastosis due to A-B-O incompatibility. Mass serum studies have resulted in the occasional detection of anti-O immune bodies, usually in low titer. None of these have resulted in clinical disease of the newborn infant. Further details are to be presented in a subsequent publication.

Until 1944 exact studies of Rh-iso-immunization were hampered by the disturbing fact that more than half of the Rh-negative women who gave birth to

erythroblastotic infants failed to demonstrate antibodies in their sera by ordinary saline agglutination techniques.[20] The detection of antibodies in such cases was facilitated following the studies of Race[21] in England, and Wiener[6] and Diamond[22] in this country. By special techniques, an antibody was shown to be present which was of definite pathogenetic significance. It is variously referred to as an "incomplete," "univalent," "blocking," or "inhibitor" antibody or "glutinin." In spite of the variegated terminology, there is no doubt as to its etiologic importance. This antibody, although adsorbed upon the red cells, fails to produce visible agglutination of erythrocytes when saline is used as the standard diluent medium. Its presence can now be detected in every instance of isoimmunization by the conglutination test, using serum, plasma, or albumin as diluents, or, more recently, by the use of a rabbit anti-human, globulin serum.[23] The use of saline suspensions is avoided in the conglutination test and its modifications.

In the 96 patients included in this series, 65, or 67.7 per cent, demonstrated only univalent antibodies; 23, or 24.1 per cent developed solely agglutinins or bivalent antibodies; while 8 or 8.3 per cent showed a mixture of both varieties (Table V).

TABLE V. TYPE OF ANTIBODIES IN NINETY-SIX SENSITIZED PATIENTS

TYPE	NUMBER OF CASES	PERCENTAGE OF TOTAL
Univalent	65	67.7%
Bivalent	23	24.1%
Univalent and bivalent	8	8.3%
Total	96	100.1%

The terminology now in use cannot be considered entirely definitive or permanent. Much remains to be learned concerning the biological properties and mode of action of these antibodies. Because of the demonstrated higher incidence of glutinins, information pertinent to their physico-chemical properties is of interest. Coombs and Race,[24] in a study of univalent antibodies, noted the following characteristics: (1) a molecular weight greater than 30,000; (2) greater thermostability than the bivalent variety; (3) their preferential adsorption by Rh antigen when added to serum which contains both types of antibodies. Wiener[25] has postulated that they have a smaller molecular weight than agglutinins and hence traverse the placenta with greater ease. He has likewise subdivided the clinico-pathologic manifestations of erythroblastosis into two syndromes dependent upon the occurrence of either univalent or bivalent antibodies in the maternal serum. Differences in therapeutic approach are a corollary of this subdivision.[9]

V. Correlation of Prepartum Antibody Titer With Neonatal Mortality

The availability of sensitive testing procedures now assures the practically universal detection of maternal isoimmunization, but gives rise to other practical clinical problems. Reference to the literature reveals only broad generalities in regard to the prognostic significance of maternal antibody titers. However, the continued demonstration that isoimmunization does not necessarily mean neonatal disease makes the establishment of some criteria imperative.

Frequent prenatal serum studies on a sufficiently large group of patients offers the only feasible method by which such standards can be established. An analysis of this type has been made in a group of 55 sensitized women (Table VI). Repeated quantitative conglutination tests were performed using serum as the vehicle for suspension of the Rh-positive test cells. In 40 patients parallel studies were also made with plasma substituted as the suspending vehicle.

Comment is made below concerning the influence of technical procedural variations on antibody titer. Twenty-seven patients in the former group had a serum titer of between one and ten units* at term. Twenty-five, or 92.6 per cent, of the infants in this group survived while two, or 7.4 per cent, died. Nineteen patients demonstrated serum conglutination titers between 10 and 100, and in this group only three, or 15.8 per cent, of the infants survived, while 16, or 84.2 per cent, died. In a group of seven patients with serum titers ranging between 100 and 1,000 units, only one infant survived and six died neonatally. Two patients were observed with an antepartum titer of over 1,000. The offspring in both instances did not survive.

Our present series is too small to warrant dogmatic inferences. However, one cannot fail to note the very definite correlation between antibody titer and outcome of pregnancy. The accumulation of further studies of this type will ultimately provide a yardstick for the guidance of the obstetrician in the management of the Rh-negative sensitized woman.

The technical aspects of the serum conglutination test which has been utilized for these quantitative studies are still in somewhat of a state of flux. Wiener believes that the visible cohesion of erythrocytes which constitutes the conglutination phenomenon is brought about by the presence of an "x protein" in the serum.[5] The substitution of plasma for serum as suggested by Wiener results usually in a higher titer. At times the plasma conglutination test may lead to the detection of a low titer of antibodies when none can be demonstrated by the serum technique. Wiener,[9] therefore, believes that the former is the more sensitive procedure. However, it should be noted that prognostic evaluation of antibody titer, as determined by the serum conglutination test, is not equivalent to a similar titer when obtained by the use of plasma. Observation of the data presented in Table VI indicates that serum conglutination titers of over 10 units connote a high incidence of neonatal mortality; whereas such serious import becomes apparent only in higher plasma conglutination titers. In the 40 patients studied by the plasma conglutination technique, significant infant mortality was noted only when maternal plasma titers were somewhat higher.

TABLE VI. CORRELATION OF PREPARTUM ANTIBODY TITER WITH NEONATAL MORTALITY IN FIFTY-FIVE SENSITIZED WOMEN—SERUM CONGLUTINATION TEST

ANTIBODY TITER (UNITS)	LIVED		DIED	
	NUMBER	PER CENT	NUMBER	PER CENT
1-10	25	92.6%	2	7.4%
10-100	3	15.8%	16	84.2%
100-1000	1	14.3%	6	85.7%
Above 1000	0	0	2	100.0%

Other vehicles for suspension of test cells have recently been suggested. Among these is bovine albumin solution.[8] Preliminary observations in our laboratory indicate an even greater sensitivity, using this technical modification. Correlation of antibody titer with neonatal disease using the latter procedure remains to be determined. Such studies are under way at present. Levine has commented recently[26] upon the use of gum acacia, certain varieties of gelatin, polyvinyl alcohol, and even commercial mucilage in the conglutination test. Quantitative data with these substances are quite scanty at present. Nevertheless, their successful use in the conglutination reaction would appear to cast doubt upon the concept that plasma or serum contains a specific substance, conglutinin or "x protein," which is necessary for completion of the antigen-antibody reaction. There is no

*The term, unit, indicates the reciprocal of the titer. Thus a serum titer of 1:10 would be expressed as 10 units of antibody.

doubt that ultimately the technique of this test will be further standardized and even more exact correlation between prepartum antibody titer and the severity of neonatal disease will be possible.

VI. The Course of Isoimmunization During Pregnancy and in the Puerperium

Because of the fact that most previous studies in Rh sensitization have been made either close to term or following the birth of erythroblastotic infants, opportunities for serial observations during pregnancy have of necessity been relatively infrequent.

Nevertheless, on the basis of available clinical and experimental evidence, there now exist at least two distinct viewpoints in regard to the phase of pregnancy particularly associated with isoimmunization. Levine[27] feels that the process may occur during pregnancy, particularly in the last trimester. Wiener[28] believes that the most potent dose of fetal antigen gains access to the maternal circulation at the time of labor, when placental rupture occurs and erythrocyte-laden villi are afforded numerous avenues of entry into the maternal blood stream.

In an effort to shed more light upon this problem, the data accumulated from the study of a group of 49 women, who were tested periodically during the course of pregnancy, were analyzed. Of the group, 27 showed significant prepartum changes in antibody titer and 22 evinced no titer changes. In the former group there are 16 women who were noted to change from a non-immunized state to one of sensitization, and in 11 this transition occurred in the third trimester. The outcome of pregnancy is known in 14 of the 16 women. There were no instances of erythroblastosis fetalis in the infants of ten. The maternal serum titer in nine of these cases was below 10 units. Erythroblastosis fetalis was present in four cases, two resulting in infant deaths associated with maternal serum titers of 12 and 24 units, respectively, the others in survival of the infant with maternal titers of two and three units, respectively.

Examination of this data leads to the inescapable conclusion that placental transfer in the absence of preceding maternal sensitization does occur during pregnancy. In the majority of cases, however, the degree of sensitization thus initiated is comparatively slight, and, as we have shown, is usually not associated with neonatal disease. Infant mortality, when it occurs, is associated with a concomitant rise in maternal antibody titer.

That the potentiality for early isoimmunization exists has been demonstrated by the discovery of Rh antigen in a 48 mm. embryo by Stratton.[29] Levine[27] has noted, as the result of analogy from animal experiments, that quantities of incompatible red blood cells as small as 0.13 c.c. are sufficient to stimulate the production of anti-Rh immune bodies. Studies on the guinea pig by Flexner and Gellhorn[30] indicate that during the latter part of pregnancy increased permeability of the placenta to water and sodium as measured by radioactive isotopes regularly exists; it would seem probable by analogy that greater opportunities for antigen transfer likewise occur during the same period.

Experimental studies, therefore, are quite compatible with the thesis that prepartum antibody changes do occur, and the present clinical study substantiates this. However, lack of sufficient numbers in the present series serve to emphasize the fact that this opinion is of a preliminary nature, and will be augmented only by subsequent observations.

Eleven patients in the group of 27 who demonstrated titer changes were found to be immunized at the time of the first serum study. The serum titers in all instances were greater than 10 units at some time prior to delivery, and in all cases erythroblastosis fetalis was present in the offspring. Fatalities occurred in nine of the eleven cases.

In the group of 22 patients who showed no titer increase during pregnancy, eleven had infants with erythroblastosis fetalis. Study of these cases reveals again a distinct correlation between prepartum antibody titer and outcome of pregnancy. Seven of the eight fatalities in this group occurred in infants where maternal serum conglutination titers were greater than 10. Eleven of the group had normal infants. The infants proved to be Rh negative in six. The remaining five women with Rh-positive babies had serum titers of well under 10 units.

Stress has recently been placed upon the total duration of the isoimmunized state prior to delivery as a determinant of neonatal disease. Page, Hunt, and Lucia[31] have found that the appearance of clinical erythroblastosis fetalis can be correlated with the total antepartum duration of maternal antibodies, when their cases were first divided into those containing small amounts of antibody, and those with larger amounts. Of 43 patients who were tested at some time prepartum in our laboratory, 19 revealed initial sensitization less than ten weeks from term, and 24 demonstrated sensitization for periods greater than ten weeks prior to delivery. In some of the latter cases, the time of initial antibody production could only be approximated because of the fact that the women were already sensitized when first studied. In the series of 19 women, only 10, or 52.6 per cent, of the infants had erythroblastosis fetalis, whereas in the latter series of 24, 17, or 70.8 per cent, of the offspring showed evidence of erythroblastosis. Actually, then, there appears to be a rough correlation between the length of time of exposure to the antibodies and the appearance of fetal erythroblastosis. That this factor is apparently only secondary to the degree of maternal isoimmunization is illustrated by the following observations: Of the group of 17 patients who showed sensitization for periods greater than ten weeks, and in which all infants developed erythroblastosis fetalis, 14 women, or 82.4 per cent, had antepartum serum conglutination titers greater than 10 units. Of 7 patients who exhibited sensitization for periods greater than ten weeks, and in which group all infants were normal, maternal antibody titers were less than 10 units.

The influence of labor upon maternal isoimmunization has been previously mentioned. In a group of 19 patients (Table VII) it was possible to compare pre- and postpartum titers. The optimum time for observation of the possible stimulating effect of a large dose of antigen has been stated to be approximately eight to twenty days postpartum.[32] Owing to circumstances beyond our control, the time of study could not be entirely regulated, and serum studies were therefore made two days to sixteen weeks after parturition.

In 11, or 57.8 per cent, of the cases, a significant rise in titer was noted, and in some instances this rise was of considerable magnitude. One of our patients went from a plasma antepartum titer of 96 to a six-week postpartum titer of 196,608 units. Another rose from a serum antepartum titer of 1,024 to a six-week post partum titer of 16,384. In no case under our observation were comparable increases noted during the course of pregnancy within a like period of time.

In summary, therefore, it may be noted that: (1) Clinically detectable isoimmunization does occur during pregnancy, particularly in the last trimester. When it occurs antibodies are usually of low titer, and are associated generally with no evidence of neonatal disease, or less frequently with varying manifestations of congenital hemolytic disease, depending upon the degree of maternal sensitization. (2) Patients who show immune bodies throughout a large portion of pregnancy, particularly if the titer is significantly increased, give birth in a high proportion of cases to infants with hemolytic disease. Degree of sensitization, however, seems to be more important than duration of sensitization. (3) Labor is a potent factor in the stimulation of maternal antibody formation.

TABLE VII. PRE- AND POSTPARTUM OBSERVATIONS OF ANTIBODY TITER IN NINETEEN SENSITIZED WOMEN

CASE NUMBER	ANTEPARTUM TITER			POSTPARTUM TITER			TIME OF POSTPARTUM OBSERVATION
	PLASMA	SERUM	SALINE	PLASMA	SERUM	SALINE	
2	96	8	0	196608		0	6 Weeks
3	2048	512	3	2048	768	2	6 Weeks
5		32	32		192	192	16 Weeks
12	24	8	0	3072	256	3	10 Days
13	2048	512	0	2048	768	0	10 Days
14	8	6	0	96	24	0	10 Days
20		16	0		16	0	5 Days
24	8192	1024	0	49152		0	12 Weeks
31		768	0		1024	0	6 Weeks
33	8	3	0	32		0	2 Days
37		64	64		64	32	10 Days
38		3	0		6	0	4 Days
42	256	96	0	384	128	0	16 Weeks
43	6	4	0	8	6	0	3 Days
46		16	0		64	0	7 Days
48		3	0		12	0	6 Weeks
50	256	128	6	2048	768	16	10 Days
62	1024	1024	1024		16384	16384	6 Weeks
74		8	0		48	16	6 Days

VII. Postpartum Persistence of Antibodies

Eighteen patients in our series were not pregnant at the time serum studies were made (Table VIII). The last pregnancy had occurred one to sixty months prior to examination. Eleven of these individuals exhibited univalent antibodies, six bivalent antibodies, and one had antibodies of both varieties. Titers varied from 3 to 49,152 units. One patient with no history of subsequent transfusion still had a titer of 128 units of univalent antibody thirty-four months after the last pregnancy. Another patient demonstrated 49,152 units of univalent antibodies three months postpartum.

TABLE VIII. POSTPARTUM PERSISTENCE OF ANTIBODIES IN EIGHTEEN CASES

CASE NUMBER	TIME POSTPARTUM OBSERVATIONS MADE (MONTHS)	TYPE AND TITER	
		UNIVALENT	BIVALENT
16	34	128	
45	18	6	
49	28		12
56	60		8
67	24	32	0
68	21		4
71	14	12	3
72	6		8
73	19	Qualitative tests positive	
51	12	Qualitative tests positive	
69	1	8	
75	8	8	
5	4		192
24	3	49,152	
33	4	384	
41	5	384	
42	4	128	
62	5		512

It is obvious that Rh antibodies in common with other immune bodies persist in the circulating blood and can be demonstrated for a long time after the initial antigenic stimulation. Davidsohn[32] demonstrated antibodies in a patient six years after she had given birth to an erythroblastotic infant. Even when antibodies are no longer demonstrable in vitro, the altered reactivity of the body can be demonstrated by an anamnestic response to repeated stimulation years after the initial antigenic stimulus. An excellent illustration of this situation is the case cited by Levine.[33] His patient, a 20-year-old Rh-negative primigravida, who fourteen years before had received several transfusions of her father's Rh-positive blood, gave birth to a hydropic infant.

It has been noted that with the establishment of an immunized state, successive pregnancies will lead to the birth of Rh-positive infants with increasingly severe manifestations of erythroblastosis fetalis.[28, 34] Our experience corroborates this observation. In a group of 14 women who gave histories of the birth of erythroblastotic infants previously, 13 were delivered of similarly affected children in the current pregnancy.

These observations tend to emphasize two points of important clinical significance: (1) the necessity of avoidance of unwitting sensitization of Rh-negative females by the administration of Rh-positive blood; (2) the relative inadequacy of routine crossmatching procedures in detecting isoimmunization. Both may be avoided by the routine administration of Rh-negative blood to Rh-negative females. Should it prove necessary in extreme emergency to give Rh-positive blood to such a patient, the conglutination technique should be substituted for the usual crossmatching procedure. This, at least, reduces the immediate danger of hemolytic reactions of varying degrees of severity.

VIII. Correlation of Parity With Initial Evidence of Rh-Isoimmunization

A clear distinction has been made between the incidence of Rh-isoimmunization and that of erythroblastosis fetalis. Our studies as well as those previously cited[14-16] indicate that sensitization may occur without the production of obvious disease in the offspring. Most previous reports have been concerned with the time of initial appearance of clinical erythroblastosis fetalis. Only by the routine prepartum serologic study of large groups of Rh-negative women is it possible to detect minute subclinical amounts of antibody.

Examination of our material reveals that isoimmunization, like erythroblastosis, is essentially a phenomenon associated with multiparity. However, it is interesting to note that our data indicate that sensitization occurs, in a high percentage of instances, at an earlier date than was hitherto realized (Table IX). Of the group of 96 sensitized women in this series, 86 were multigravidas and ten were primigravidas. Six of the ten primigravidas had a definite history of prior transfusion. In the remaining four no such history could be elicited. The possibility of iso-immunization still exists in these instances, perhaps associated with a forgotten injection of whole blood intramuscularly in childhood as suggested by Levine.[33] All infants in this group of primigravida survived and in only three were there mild evidences of hemolytic disease. Again it must be emphasized that in all instances but one, maternal antibody titers were below 10 units. The one patient with an antibody titer of 32 gave birth to an Rh-negative baby and it is certain that the immune bodies found were remnants of previous sensitization.

In multigravida the initial appearance of isoimmunization was gauged by the folowing criteria: (1) the detection of antibodies during the current pregnancy, and (2) an unmistakable history of hemolytic disease in a previous pregnancy. A number of patients in this group gave histories of early spontaneous

TABLE IX. CORRELATION OF PARITY WITH INITIAL EVIDENCE OF RH-ISOIMMUNIZATION IN EIGHTY-FOUR MULTIGRAVIDA

PREGNANCY	NUMBER OF WOMEN	PERCENTAGE OF TOTAL
Second	41	48.8%
Third	12	14.3%
Fourth	13	15.5%
Fifth	2	2.3%
Sixth	9	10.7%
Seventh	2	2.3%
Eighth	3	3.6%
Ninth	1	1.2%
Tenth	0	0.0
Eleventh	1	1.2%
Total	84	99.9%

abortion, fetal death in utero, or even stillbirths of undetermined etiology. These were not considered due to Rh-isoimmunization. It can thus be readily seen that the estimation of onset of isoimmunization will err, if anything, on the conservative side since some of these mishaps may have been definitely associated with Rh sensitization. Of the group of 86 multigravida, two were not available for this analysis. In 41, or 48.8 per cent, of the 84 multigravida the initial evidence of isoimmunization appeared in the second pregnancy. Initial isoimmunization in the remaining 51.2 per cent was scattered from the third to eleventh pregnancy.

No data exist in the literature at present concerning the future course of women with what may be termed minimal or subclinical Rh sensitization. It should be of great theoretical and practical interest to study the serologic behavior, in subsequent pregnancies, of the 19 patients in our series who fall into this group. At the time of writing a few such women have returned, again pregnant, for further serum studies.

Discussion

Routine prenatal Rh typing was done on 12,275 women during a thirteen-month period beginning Aug. 1, 1945. Analysis of this mass data has already yielded information of practical clinical import. In some instances the information obtained added numerical support to previous observations. Thus, the distribution of Rh types in our group corresponds closely to previously established ratios. Of great interest has been the demonstration of the incidence and behavior of Rh-isoimmunization. Current methods of serum study permit the virtually universal detection of this phenomenon. It should be noted that only the performance of serial antepartum studies permitted the detection of many instances of sensitization which would otherwise have been overlooked because antibodies were of insufficient magnitude to lead to clinically detectable disease in the newborn infant. The ultimate importance of the early detection of isoimmunization will only become manifest within the next several years as these women became pregnant again. Information can then be accumulated regarding the rapidity of development of antibody titers of sufficient degree to lead to clinical neonatal disease. Furthermore, one may then be permitted to test the thesis concerning individual variation in immunizability. Generalization on the influence of multiparity upon the incidence of erythroblastosis fetalis can be replaced by factual data.

Aside from the definite etiologic role of Rh-isoimmunization in the causation of frank erythroblastosis fetalis, the relationship of this immune state to other pathologic phenomena associated with pregnancy or occurring in the infant is at best indefinite. The current belief, for example, that Rh heterospecificity has little, if anything, to do with the occurrence of spontaneous abortion is based largely upon work done prior to the introduction of the more sensitive tests for isoimmunization. It will be of interest to reexamine this issue in the light of further more complete data. Preliminary examination of our material indicates a statistically significant higher incidence of spontaneous abortion in Rh-negative sensitized women.[35] Among other problems in need of restudy with more sensitive techniques may be mentioned the relationship of undifferentiated mental deficiency and so-called physiologic icterus to subclinical sensitization.

Our studies subtantiate the greater antigenic potency of the Rh_0 factor which is operative not only in pure Rh-negative women, but also in those individuals belonging to the uncommon Rh-positive categories, Rh′, Rh″, and Rh′R″. The data presented also demonstrate clearly the marked predominance of so-called univalent antibodies in the serum of isoimmunized women. There is a distinct need for more fundamental studies of this immunologic phenomenon. Such investigations may have an important bearing on other aspects of clinical immunology.[36, 37] Information concerning the mechanism of the hemolytic action of univalent antibodies is urgently needed. Studies of this nature are in progress here.

With the adoption of routine prenatal serological study of Rh-negative pregnant women, the necessity for establishment of quantitative antibody data of prognostic significance becomes evident. This has been dealt with in some detail in the present study. It is recognized that the group of cases is relatively small. Nevertheless, the inverse ratio between elevation of titer and survival of offspring seems significant.

The fluctuating technical status of the conglutination test at present leaves much to be desired. The rapid succession of suspending vehicles for the test cells has undoubtedly resulted in increased sensitivity of the procedure. The longest experience has been with serum suspended cells and hence this procedure, at the moment, offers a more certain foundation for prognostication based on antibody titer. However, the routine use of bovine albumin solution, which has proved very sensitive in our hands, may eventually supplant other techniques.

No attempt has been made in this paper to discuss either the morbid anatomic features of erythroblastosis fetalis or its therapy. In spite of the clarification of many of the basic mechanisms in this disease within the past five years, the mortality still remains quite high. Almost two-thirds of the erythroblastotic infants delivered by isoimmunized women in the present series died. This may be due in part to an insufficient understanding of the physiologic and biochemical abnormalities which exist in these afflicted infants. In part, it is also, undoubtedly, due to irreversible damage to the fetus by the time it is born. Lack of a standardized therapeutic technique is certainly an important contributing factor. The long range view, it would seem, demands an attack upon the problem from a preventive standpoint.

Summary

1. During the first thirteen months of operation of this laboratory, Rh typing was performed as a routine part of prenatal care on 12,140 women. One hundred and thirty-five additional known Rh-negative women were referred for detailed serum studies. The distribution of Rh types in the former group conformed closely to previously established ratios.

2. In a group of 1,635 Rh-negative women whose husbands were Rh positive, 86 instances of isoimmunization, or 5.26 per cent, were observed.

Among 1,635 Rh-negative women there were 727 primigravidas and 908 multigravidas. Nine instances of isoimmunization, or 1.24 per cent, were observed among the primigravidas. Seventy-seven sensitized multigravidas were observed, an incidence of 8.48 per cent.

3. Nine instances of isoimmunization were encountered in women belonging to types Rh′ or Rh″. This constituted a theoretically calculated incidence of 5.7 per cent. It was noted that individuals of these blood types behaved, to all intents and purposes, as if they were pure Rh negative.

4. One instance of Hr isoimmunization was encountered in a group of 10,500 Rh-positive women.

5. Erythroblastosis fetalis occurred in the offspring of 53, or 67.1 per cent of 79 isoimmunized women. Erythroblastosis fetalis was absent in the infants of 26, or 32.9 per cent, of this group. The fact was emphasized that the presence of Rh-isoimmunization was not necessarily synonymous with hemolytic disease in the offspring.

6. Erythroblastosis fetalis occurred once in 215 deliveries, an incidence of 0.46 per cent, in the total group of 12,275 women studied.

7. Antibody specificity was studied in 38 cases. Anti-Rh_0 immune bodies were found in 32. Four patients had antibodies of Rh_1 specificity; one, anti-Rh_2; and one, anti-Hr′.

8. In 65, or 67.7 per cent, of 96 patients only univalent antibodies were found. Twenty-three, or 24.1 per cent, developed only bivalent antibodies. Eight, or 8.3 per cent, showed a mixture of both varieties.

9. Fifty-five patients were studied in an effort to correlate prepartum antibody titers with outcome of pregnancy. When serum conglutination titers exceeded 10 units a significant infant mortality was noted. In 40 patients who were studied by the plasma conglutination technique, significant infant mortality occurred only when maternal titers were somewhat higher.

10. In a group of 49 patients in whom repeated prepartum serum studies were made several categories were observed: (a) sixteen patients changed from a nonimmunized state to one of sensitization. In 11 this occurred in the last trimester; (b) eleven patients who were immunized when first studied showed a significant rise in titer during pregnancy; (c) twenty-two patients displayed no titer increase during the entire prenatal period. A distinct correlation between maternal serum titers and neonatal disease was demonstrated in most instances.

11. The influence of labor on antibody titer was studied in 19 patients. Eleven, or 57.8 per cent, showed a significant rise in titer.

12. The duration of existence of the prepartum isoimmunized state, although of significance, was felt to be less important pronostically than the antibody titer.

13. Eighteen patients who were observed one to 60 months post partum were demonstrated to still have antibodies in the circulating blood. The significance of this fact for transfusion therapy and subsequent pregnancies was noted.

14. Of 96 isoimmunized women, ten were primigravidas and 86 multigravidas. Six of the ten primigravidas had a definite history of previous transfusion.

15. In 48.8 per cent of the multigravidas, the initial evidence of isoimmunization occurred with the second pregnancy. Initial isoimmunization in the remaining 51.2 per cent was scattered from the third to the eleventh pregnancy.

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THE PLACENTAL STAGE AND POSTPARTUM HEMORRHAGE

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IN AN article "Blood Transfusion and Obstetric Hemorrhage" published in 1935, I stated that the mortality from obstetric hemorrhage had not decreased in the last twenty years despite the use of blood transfusion. Another twelve years have passed and we are in the "Age of Atomic Energy," and yet women still die from hemorrhage associated with parturition. Hemorrhage caused 30 per cent of the maternal deaths which occurred in the United States in 1944 and 1945. These deaths were either preventable or had preventable factors. It is difficult to determine just how many of the deaths were due to postpartum hemorrhage. Some of the patients do not die from the hemorrhage, but their resistance is lowered to such a degree that they succumb to infection. Pastore stated that the incidence of puerperal infection increased 400 per cent if the hematocrit dropped below 30 per cent. Reports of the Children's Bureau indicate that approximately 20 per cent of the women delivered in the last trimester of pregnancy have a postpartum hemorrhage, and of these about 40 per cent die primarily from hemorrhage and shock. A report of the maternal deaths in Philadelphia indicated that over 5 per cent were due to postpartum hemorrhage.

Beecham, in 1939, stated that in a six-year period in Philadelphia, 52 women died from postpartum hemorrhage, and that 62 per cent of these deaths were preventable. He stated, "The usual story was not that of sharp, marked hemorrhage for a few minutes and then sudden death. Rather the picture brought to light by this study was one of steady, moderate bleeding over a period of several hours ending in shock and death because no one became alarmed. There was an occasional case where bleeding was sudden and great in volume with the patient going into shock rapidly, but even in such a case there was usually time for adequate treatment." He stated that the average time between delivery and death was five hours and twenty minutes, long enough for treatment. Similar comments are made by the Chicago Maternal Death Committee.

Data from representative obstetric services given in Table I indicate that the incidence of postpartum hemorrhage is somewhere between 2 and 3 per cent, and, even in these well-regulated institutions, deaths from postpartum hemorrhage, although rare, occur. During the past fifteen and one-half years we have had four deaths from postpartum hemorrhage, and during a similar period at The New York Lying-In Hospital they had eight deaths. During the past five years at The Boston Lying-in there have been four deaths from

Eli Lilly & Co., supplied 1 ml. ampules containing 1 unit of solution of posterior pituitary.

postpartum hemorrhage. In almost every instance there were other complicating factors and the patient in these hospitals was not permitted to bleed to death without any attention. Nevertheless, the deaths in most instances had preventable factors.

Our studies indicate that proper conduct of the late second and early third stages of labor caused a marked reduction in the incidence of postpartum hemorrhage due to uterine atony, excluding patients who had a placenta previa or an abruptio placenta. We wish to stress the importance of a definite routine for the prevention and treatment of postpartum hemorrhage which will reduce the mortality to almost zero.

For many years the proper conduct of the third stage has been to wait for Ahlfeld's signs of separation of the placenta, and the usual instructions are to wait fifteen minutes to two hours or longer. Some clinicians still cling to these teachings. Warnekros in 1918 and Weibel independently in 1919, demonstrated by means of x-ray studies taken immediately (one to two minutes) after delivery, that the placenta was separated within less than five minutes after the delivery of the baby. Each investigator found little evidence of retroplacental hematoma which is supposed to separate the placenta.

Calkins, Davis, Leff, Titus, and numerous other investigators have reported that the placenta separates and can be expressed within one to seven minutes after the birth of the baby. These various reports are based on observation of thousands of cases or on actual palpation of the interior of the uterus (Leff).

Davis stated that, on our service, 16 per cent of the cases of fatal postpartum hemorrhage were due to retained placental tissue, and 36 per cent to atony (no other demonstrable cause). This latter group is much larger in the nonfatal cases and are of particular concern because a properly conducted second and third stage of labor will prevent almost all of these hemorrhages. Peckham and Kieder found that 81 per cent of the cases of hemorrhage were due to atony.

Hemorrhage from the placental site is controlled, (1) by the contraction of the uterus (compressing the uterine vessels); (2) by the time the contraction is over, retraction of the muscle bundles has occurred and the vessels are permanently compressed, and (3) by clotting of the blood in these vessels. If there is no retraction—complete loss of muscle tone—bleeding will recur each time that the contraction is over, for no uterus can remain in a state of constant contraction.

Unfortunately, most clinicians still ascribe postpartum hemorrhage to mismanagement of the third stage of labor. Davis and Boynton in 1941 are the first, so far as we know, to state that the proper management of the third stage begins in the late second stage of labor. They reported that, if 0.2 mg. of ergotrate were given intravenously after the delivery of the head or of the anterior shoulder, and thirty seconds allowed for its action, in 72 per cent of their cases the placenta had separated and could be expressed within three minutes. They attributed this short third stage to the use of intravenous

ergotrate in the late second stage. However, all the evidence at hand indicates that the placenta normally begins to separate as the baby is born and that it can be expressed usually within one to three minutes after delivery. If the women were in the upright or squatting position, gravity would cause the early delivery of the placenta. With the patient in the supine position and usually anesthetized, external force must be used to expel the placenta.

The so-called Duncan and Schultze methods of placental separation and extrusion from the uterus are only of historical interest, and discussion should be omitted from textbooks. The retroplacental hematoma is almost nonexistent if the second and third stages are properly conducted, and most obstetricians now know it has nothing to do with placental separation. We have confirmed Royston's statement that if the placenta is extruded through a tight ring (contracted uterus or vaginal orifice), it will almost invariably be a Duncan, and vice versa.

TABLE I. POSTPARTUM HEMORRHAGE

HOSPITAL	YEAR	DELIVERIES	HEMORRHAGE INCIDENCE PER CENT	MORTALITY (CASES)
Johns Hopkins	1933	19,290	6.14	4 deaths in series (corrected)
Boston Lying-in	1941-45	13,347	1.71	2 deaths
New York Lying-In	1936		6.40	
New York Lying-In	1940-43	9,040	1.94	6 deaths 1932-42 2 deaths 1943-45
Chicago Lying-in	1933-36	8,100	2.50	4 deaths 1931-42 0 deaths 1943-46
Chicago Lying-in	1941	753	2.00	Ergotrate in third stage
Chicago Lying-in		1,020	0.40	Ergotrate with anterior shoulder
Chicago Lying-in	1944-46	6,638	2.50	Ergotrate with anterior shoulder
Chicago Lying-in	1946—6 mo.	664	1.36	Ergotrate with anterior shoulder
Chicago Lying-in	1946—6 mo.	1,159	0.35	Solution posterior pituitary with posterior shoulder

Davis' technique has been the routine on our service up to the present time, but patients still continue to have postpartum hemorrhage. As indicated in Table I, the incidence for 6,638 vaginal deliveries in 1944 to 1946 was 2.5 per cent. It is true, as pointed out by Davis, that we rarely have to pack uteri for postpartum hemorrhage since using intravenous oxytocics. However, all of us—including Davis—have had patients who, despite intravenous injections of an oxytocic drug, continued to bleed from the atonic uterus. Since we still have postpartum hemorrhage due to atony and, it seems to us, a higher incidence of delayed hemorrhage occurring five to twenty days after delivery, we began to restudy the conduct of the late second and third stages of labor.

Leff, in 1945, reported that the action of ergotrate was different from that of solution of posterior pituitary, and believed that the latter solution was preferable until the placenta had been expelled from the uterus. A number of investigators have compared the effects of intravenous injections of ergotrate with intramuscular injection of pituitary solution. No one, so far as we know, has injected both of these oxytocics intravenously. Numbered

solutions of unknown content were given to the resident staff for intravenous injection during the late second and third stages of labor. These solutions either contained saline solution, 0.2 mg. of ergotrate, or one or two units of solution of posterior pituitary. The study was carried out in six-month periods in 1944, 1945, and 1946.

The data in Fig. 1 illustrates that the placenta had been expressed within nine minutes in almost all cases irrespective of the time or substance injected. These studies, with the exception of the large series of 439 patients, were made by the resident, V.M.W. The large group were delivered by all members of the resident and intern group, with only a very few by staff obstetricians.

TABLE II. DURATION THIRD STAGE OF LABOR—PATIENTS PER CENT

	INTRAVENOUS INJECTION OF 1 ML. OF:									
	AFTER 2ND STAGE		AFTER DELIVERY OF ANTERIOR SHOULDER			AFTER POSTERIOR SHOULDER AND SLOW DELIVERY OF FETUS				
								SOLUTION POST. PIT.		
LENGTH MINUTES	ERGOTRATE 0.2 MG.	SOLUTION POSTERIOR PITUITARY 2 UNITS	NACL SOLUTION	ERGOTRATE 0.2 MG.	SOLUTION POSTERIOR PITUITARY 2 UNITS	NACL SOLUTION	ERGOTRATE 0.2 MG.	2 UNITS	1 UNIT	1 UNIT
0.2-1.0	6	13	7	30	29	13	35	43	50	42
2	42	41	36	33	39	50	40	35	22	29
3	30	28	19	23	18	27	15	14	18	12
1-3	78	82	62	86	86	90	90	92	90	83
4-6	17	15	28	8	9	5	5	8	10	13
7-9	5	1	10	2	5	5	3			2
10-14		1		2			2			1
15-19		1								1
20-29				2						2*
Number patients	34	61	56	44	73	44	40	80	40	439
Average time—minutes	3.6	2.6	2.7	2.1	1.9	2.6	1.9	2.0	2.0	
Average blood—ml: with placenta	136	49	95	32	55	60	55	48	40	51
After placenta						171	120	64	89	73

*Manual removal in two cases.

The figures for the duration of the third stage are given in Table II and are included to show that over 75 per cent of the placentas had been expressed within one to three minutes irrespective of time or substance injected providing the operator had been taught the proper management. If no oxytocic was used and no definite pause made in the delivery of the baby, the placenta had separated and delivered within three minutes in 80 per cent of the cases. If an injection was made with the anterior shoulder and thirty seconds allowed for its action, the placenta was delivered within three minutes in 62 per cent of the cases where saline was used and 100 per cent at the end of nine minutes. Similar figures for ergotrate and pituitary are 86 per cent at the end of three minutes and 94 per cent and 100 per cent, respectively, at the end of nine

minutes. Obviously in the majority of cases the oxytocic had no effect in the separation or delivery of the placenta.

Slow delivery of the fetus seemed to be the factor which favored the separation of the placenta. Obviously the uterine wall requires some time to readjust itself to the decreasing size of its cavity as the baby is expelled. Our next experiment was to deliver the anterior shoulder, wait thirty seconds, deliver the posterior shoulder, inject 1 c.c. of the unknown solution, wait thirty seconds, and then slowly deliver the baby. The baby was removed, and usually the placenta could be expressed without any difficulty. It has required considerable effort to keep the house staff from hurrying the delivery of the baby once the head has been born.

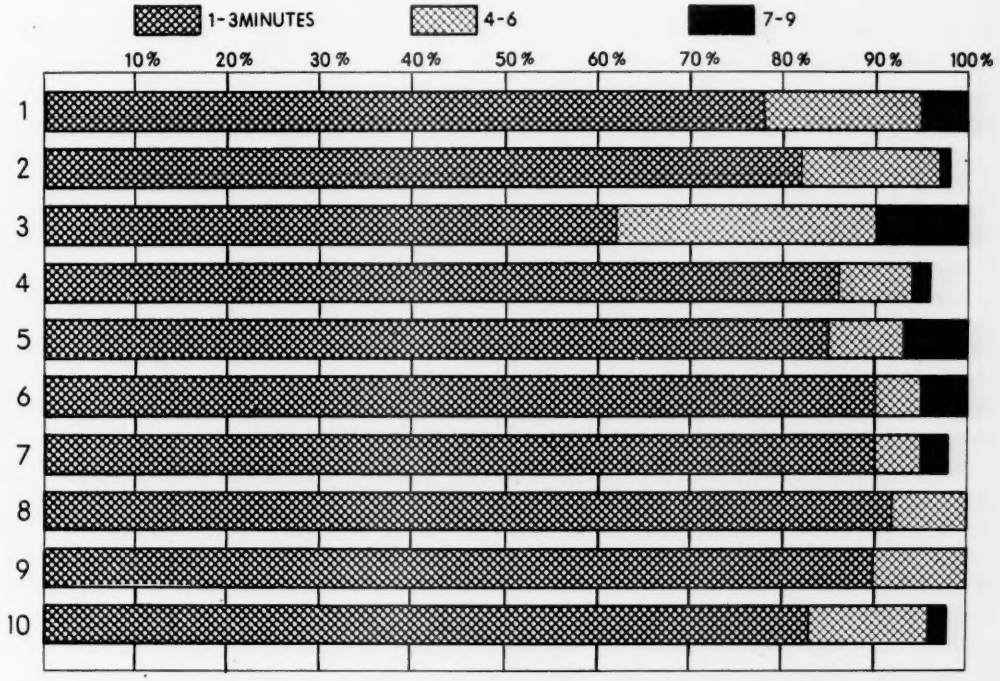

Fig. 1.—The duration of third stage of labor. Per cent of patients. Intravenous injection after second stage. 1. Ergotrate 0.2 mg. 2. Solution of posterior pituitary 0.2 ml. (2 units), after anterior shoulder. 3. Saline solution. 4. Ergotrate 0.2 mg. 5. Pituitary 0.2 ml., after posterior shoulder. 6. Saline solution. 7. Ergotrate 0.2 mg. 8. Pituitary 0.2 ml. 9. Pituitary 0.1 ml. 10. Pituitary 0.1 ml. and 0.4 mg. ergotrate intramuscularly after third stage.

Since most of our patients are anesthetized, the strength and frequency of the uterine contractions and especially the use of the abdominal muscles are minimal. Where the patient is given only gas with each pain and no traction is made on the baby, the total time from the delivery of the head to the complete expulsion of the baby requires on an average in multiparas four and one-half minutes. The average slow delivery time for primiparas under anesthesia is three and one-fourth minutes with the technique described. The placenta was delivered in 90 per cent to 92 per cent of the cases within three minutes after the delivery. Usually the placenta was in the lower segment and vagina within less than one minute and could be readily extracted without any difficulty with a minimal blood loss.

Our studies indicate that the separation and delivery of the placenta in anesthetized patients can be completed in over 95 per cent of the cases within six minutes after delivery with or without any oxytocic drug if the baby is delivered slowly. However, if no oxytocic is used either during the second or third stage of labor in these patients, the amount of blood lost with the placenta is slightly increased and the blood loss after the expulsion of the placenta is definitely increased. It, therefore, is obvious that anesthetized patients must be given an oxytocic.

Stander does not mention any length of time for the actual delivery of the baby. He states that the placenta begins to separate as the baby is born. According to him the average length of the third stage is four to seven minutes, but he also states that one should wait at least one hour for the delivery of the placenta, during this time trying repeated Credé maneuvers under anesthesia, if necessary.

Greenhill writes that after delivery of the baby's head one should wait for uterine contractions to help with the remainder of the baby, this requiring maybe one or two minutes. After delivery of both shoulders, the rest of the baby is born with one pain. He states, "Do not pull it out, but let the uterus expel it." According to him the placenta separates in a few minutes but he also advises waiting one hour, repeatedly trying the Credé expression.

Beck states that the shoulders should deliver spontaneously unless the patient is anesthetized. If there are no signs of placental separation in one hour, he advises the Credé maneuver. The placenta, according to him, should be delivered in three to four hours. No times are given for the delivery of the baby and no time for the length of the third stage.

Calkins states that in 69 per cent of the cases it was separated in less than five minutes.

The doctor must watch the uterus closely, and as soon as Calkin's sign is present—persistence of a globular uterus—the placenta is expressed by the Pastore technique with slight traction on the cord once the placenta is in the vagina. If one waits too long, the muscular portion of the uterus may contract about a portion of the placenta and make the expression difficult. If this happens, the placenta which is almost always protruding into the upper vagina, can be grasped with the sterile gloved hand and gently extracted. All placentas are removed manually if necessary at the end of one hour maximum, and usually within fifteen minutes. *If there is hemorrhage, the placenta is expressed or removed manually at once.*

Ninety per cent of 900 patients had a third stage of three minutes or less, and in 98 per cent of some 2,000 patients, it was less than nine minutes.

Davis and Boynton stated that in 1,020 patients who received an intravenous injection of ergotrate with the anterior shoulder, 81 per cent had a measured (with a graduate) blood loss of less than 100 ml. with the placenta. Only four, or 0.4 per cent, lost more than 500 milliliters. Seven hundred fifty-three patients received the ergotrate after the second stage, and only 35 per cent lost less than 100 milliliters. Two per cent lost more than 500 milliliters.

Fig. 2 shows that 95 per cent of the patients on whom the oxytocic was used after the posterior shoulder with slow delivery of the fetus, had a blood loss with the placenta of less than 100 c.c. with no postpartum hemorrhage, and 44 per cent had less than 100 ml. after the placenta, again with no postpartum hemorrhage. It is obvious that one must be very cautious about interpreting results; for example, saline solution with the anterior and posterior shoulders resulted in 75 and 81 per cent respectively, of the patients having less than 100 ml. However, the percentage of patients with blood losses of 200 ml. and more was increased. Ergotrate and pituitary are obviously better than saline.

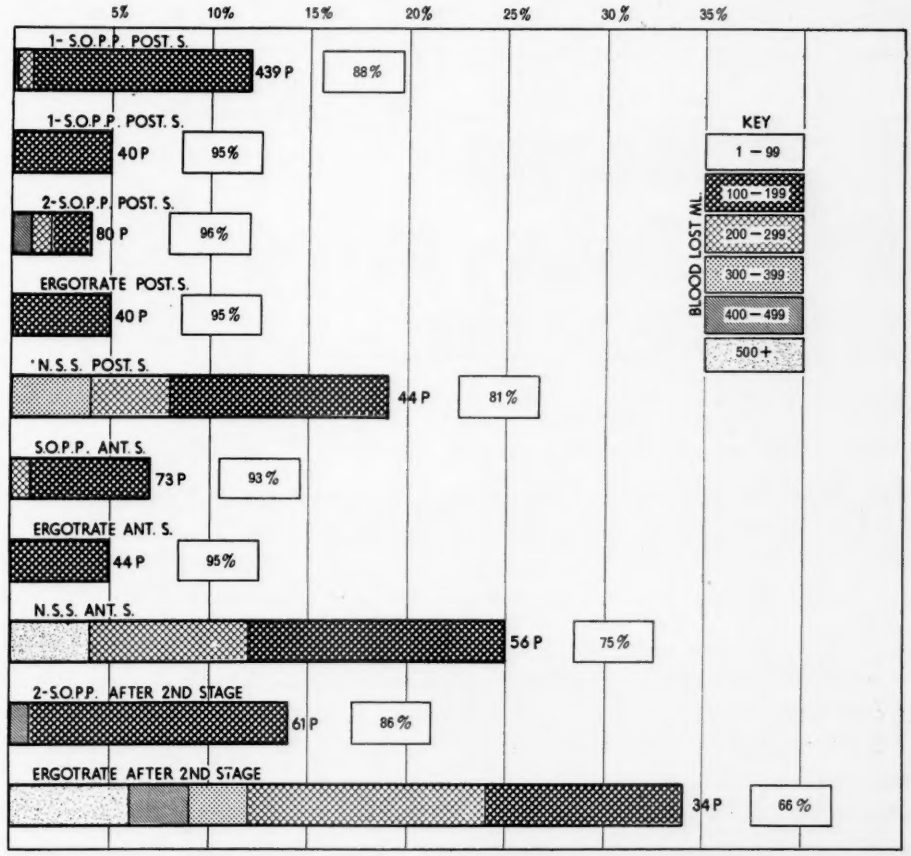

Fig. 2.—Measured blood loss with placenta. Per cent of patients. Intravenous injections.

The average blood loss for each substance used is given in Table II. The loss was less than 100 ml. for all substances, including saline if there was some delay in the delivery of the fetus. Pituitary after the second stage resulted in an average blood loss of 49 ml., while ergotrate had 136 milliliters. Davis has stated that ergotrate is more effective if injected during the second stage than after delivery. Our data indicate that the effective reduction of blood lost with the placenta is due to the pause during the delivery (Davis tech-

nique) rather than to the ergotrate. Intravenous injections of pituitary solution are active at any time during labor or the early puerperium.

Fig. 3 illustrates the percentage of patients with uterine blood loss occurring during the five to sixty minutes after the placenta had been expressed. This uterine blood is in addition to the placental blood. The relaxation of the uterus (partly due to the anesthesia) when saline was used, resulted in increased bleeding with 2 per cent having postpartum hemorrhage, and an additional 12 per cent losing 300 to 499 ml. The large series of 439 patients delivered by various members of the house staff offers the best illustration of the value of pituitary and slow delivery of the baby. Ninety-three per cent of the patients lost less than 200 ml. of blood, and 78 per cent lost less than 100 milliliters. The average blood loss with the placenta was 51, and after the placenta, 73, a total of 124 milliliters.

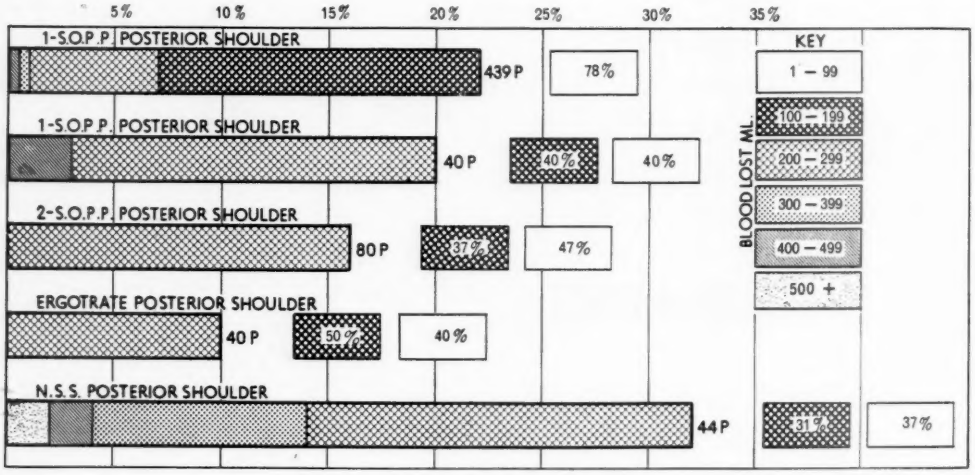

Fig. 3.—Measured blood loss after the placenta. Per cent of patients. Intravenous injection after posterior shoulder.

We had been using two units or 0.2 ml. of pituitary solution. The dose was decreased to one unit in 1 ml. of normal saline (1 ml. pituitary or pitocin and 9 ml. saline) and the final series of 439 cases was as outlined with the injection of one unit of pituitary after the posterior shoulder and, after the placenta was delivered, the injection of 0.4 mg. of ergotrate intramuscularly. There were no postpartum hemorrhages with the placenta or after the placenta, but there were a few cases of hemorrhages of 300 and 400 c.c. The number is extremely small and the blood could have come from the episiotomy or from vaginal or cervical lacerations. Some unquestionably came from the uterus which in certain cases relaxes—especially if the patient is deeply anesthetized. However, the results on the whole were better than they had been in the past.

The data in Fig. 4 are based on an exact determination as acid hematin and conversion into ml. of patient's blood of all the blood lost with the placenta and during the first hour post partum (vaginal pack) with various

methods of managing the second stage and with different oxytocic drugs. The data shows that the amount of blood lost with the placenta is greatest with rapid delivery of the fetus without an oxytocic, and that as the delivery of the fetus is prolonged and, especially if oxytocics are used, the blood loss becomes minimal. Pituitary seems to be slightly better than ergotrate, but the number of cases is too small to warrant any conclusion. It has seemed to us that 0.2 mg. of ergotrate intravenously is too small a dose, and all patients are now being delivered with the slow technique but using 0.4 mg. of ergotrate intravenously after the posterior shoulder and the same dose intramuscularly after the delivery of the placenta. Our object is to determine the best drug which will aid in preventing postpartum hemorrhage. We believe the conduct of the third stage entails the slow delivery of the baby if there are to be no complications with the placenta.

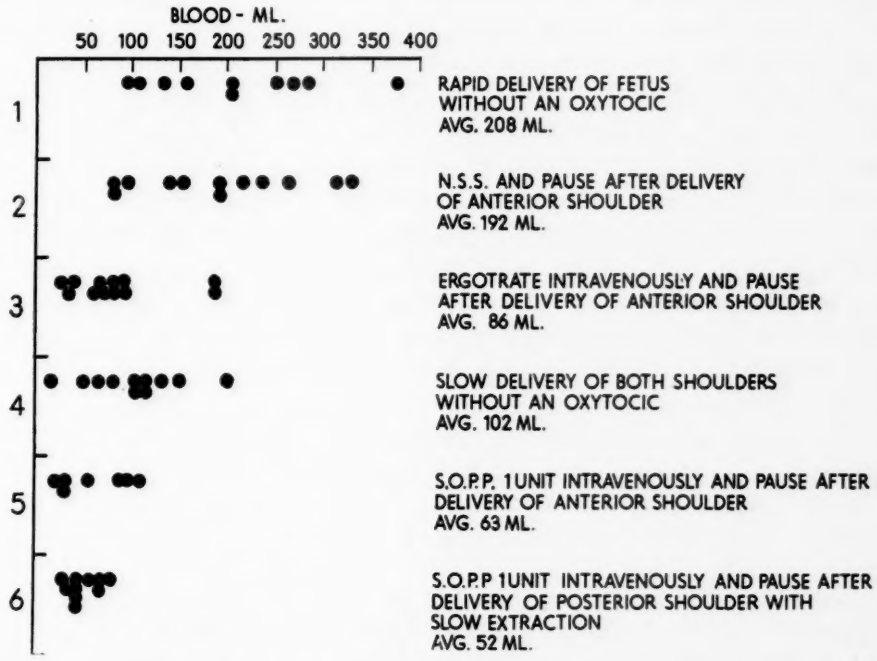

Fig. 4.—Acid hematin determination of blood lost with placenta and on packs for one hour after delivery under various managements of the late second and third stages of labor.

Davis and Boynton reported in 1941 that the incidence of postpartum hemorrhage in 753 patients who received no oxytocic in the second stage was 2.0 per cent as compared with 0.4 per cent in 1,020 patients who were given 0.2 mg. ergotrate intravenously with the anterior shoulder. This technique has been followed but the incidence of hemorrhage was 2.5 per cent in vaginal deliveries in 1944 to 1946. Pastore has defined postpartum hemorrhage as a blood loss amounting to 1 per cent or more of the body weight. Our criteria has always been 500 ml. or more, and we believe all blood losses of 300 ml. or more are abnormal. During the last six months of 1946, 1,159 patients were delivered by the house staff, using one unit of pituitary with the posterior

shoulder, and the incidence of postpartum hemorrhage was 0.35 per cent as compared with 1.36 per cent in 664 patients delivered by the staff obstetricians. Obviously the figures are similar to those obtained by Davis in 1941. Whether the decrease is again due to the special emphasis on the third stage or whether pituitary solution with the posterior shoulder is responsible, can only be determined over a period of years. We believe that intravenous injections of pituitary are much more efficacious in producing uterine contractions than ergotrate, but the latter has a longer action. *Nothing is gained by waiting hours for the separation of the placenta and our resident staff is instructed, if there is no bleeding, to remove the placenta manually within one hour at a maximum and usually within fifteen minutes after delivery.* The only exception to this rule is where there is very definite evidence of external infection on or about the vulva such as extensive contamination of the perineum with feces, a Bartholin abscess, etc.

The senior author has been advocating manual removal of the placenta as a teaching procedure for many years, and during the past six months there were 80 manual removals of the placenta and 12 explorations of the uterus; in the same period a year ago there were 18 manual removals and two explorations. The majority in the recent period were for teaching purposes. The hospital morbidity was 7.9 per cent, and for the same period in 1945, 9.2 per cent. We believe that the only way one can learn how to remove the placenta manually is to do it in normal cases under supervision. If doctors would learn this procedure, they would not be removing omentum and intestine mistakenly for placenta. They would also be able to recognize the rare case of adherent placenta; inversion of the uterus, incomplete rupture of the uterus, and myomas within the uterus.

Dieckmann and Daily reported in 1935 that the average total blood loss (episiotomy plus uterine) was 342 milliliters. Odell and Seski, in a study on our service, found that the average blood loss from an episiotomy was 253 milliliters. They found an average blood loss of 16 to 57 ml. per minute with a total blood loss of 28 to 339 ml. just from the episiotomy. Our data indicate that most patients lose approximately 51 ml. with the placenta and 73 ml. after the placenta; and, if there has been an episiotomy or extensive laceration, an additional 250 ml. or more making a total of approximately 370 ml. or more of blood in presumably normal deliveries (episiotomy). The pregnant woman does not have an extra supply of blood which will permit her to lose excessively at delivery. The withdrawal by venisection of 500 ml. of blood from patients immediately after delivery can be detected by changes in the blood within five minutes, and within twenty-four hours each patient showed an appreciable drop in hemoglobin, hematocrit, and serum protein concentration. These two facts indicate that a slightly excessive amount of blood loss at delivery will inevitably mean that the total blood loss is well over 500 ml. of blood.

All the vulvar pads, as well as the thick pads that are placed beneath patients, were saved for a period of twenty-four hours and the blood within them determined as acid hematin. The average blood loss for a large number

of patients during the first twenty-four hours after delivery, excluding the first hour, amounted to an average of 52 milliliters. Since the bleeding after the first twenty-four hours becomes negligible, amounting to only a few ml. of blood per day, no comparison of oxytocic drugs was made.

If the placenta has been delivered *intact* and yet bleeding still continues from the uterus, the following treatment is indicated:

1. Repeat the intravenous injection of ergotrate or pituitary solution.
2. Explore the uterus manually for an accessory placental lobe, tumors, and to exclude rupture.
3. Briskly massage the uterus through the abdominal wall.
4. Pack the uterus if bleeding continues despite 1, 2, and 3.

This systematic treatment will control uterine bleeding from atony in almost 100 per cent of the cases.

5. After the hemorrhage, the patient must be given saline solution, 1,000 to 2,000 ml., by hypodermoclysis and blood in amounts more than sufficient to replace what was lost (minimum 1,000 ml.), which is always underestimated. Serum, plasma, 20 per cent glucose and saline solutions, are only stop-gaps until blood is available. If 500 ml. of any of these solutions are injected intravenously, the blood pressure will increase and the patient improve, but the injection must not be repeated unless blood is also given.

Studies of postpartum hemorrhage occurring after the tenth day are still being continued. During the last six months of 1946 there was one curettage because of hemorrhage two weeks post partum. In preceding similar periods, the number has varied from five to twelve. Manual exploration of the uterus in these patients was given up many years ago because of the high mortality from infection. The uteri are curetted with a large dull curette. Only in rare instances has a piece of placental tissue been found. The usual finding is thrombosed vessels from the placental site. We think the delayed postpartum hemorrhage may be due to faulty involution of the placental site resulting from the ergotrate.

There have been several reports about the dangers of shock and death from injections of solution of posterior pituitary. In a rather long period of full-time obstetrics, the senior author has encountered one patient who is unusually sensitive to pituitary. He has seen infrequent reactions from this drug but none fatal or alarming other than those due to rupture of the uterus from tetanic contraction. In the present study, over 2,000 patients have received one or two units of pituitary during the terminal portion of the second or third stage of labor, and there have been no recorded reactions attributable to the drug.

Summary

The prevention of postpartum hemorrhage is much easier than the treatment. Prevention begins with the proper conduct of the terminal phase of the second stage of labor. With patients under analgesia, anesthesia, and on hospital beds, etc., one can no longer speak of normal deliveries. However, if

one imitates the normal mechanism of labor, results will be markedly improved. For a proper separation of the placenta, it is of the utmost importance that the baby be delivered slowly—in stages with a thirty to sixty second pause after the delivery of each shoulder—requiring a total of at least three minutes. Thus the uterine wall is given time to *contract and retract* thereby tearing itself away from the placenta. The latter has usually separated within less than one minute. After the fetus has been expelled, and as soon as the uterus retains its globular form, it should be compressed but not pushed into the pelvis. When the placenta is in the vagina it should be extracted by pulling on the cord. We do not believe that an oxytocic is necessary for the separation of the placenta; but, since patients are not under normal conditions —anesthesia, etc.— we believe that one unit of solution of posterior pituitary or 0.2 to 0.4 mg. ergotrate should be injected intravenously after the posterior shoulder if the doctor is experienced; if he is not, then after the delivery of the placenta. This will prevent excessive bleeding after the placenta. Our nurses give many of the intravenous injections.

If the placenta cannot be delivered and there is no bleeding, one may wait, at a maximum one hour, but all retained placentas should be manually removed at the end of this time.

Uterine hemorrhage is treated by the immediate removal of the placenta, manually if necessary, or after the third stage by manual palpation of the uterine cavity and visual inspection of the vagina and cervix. One of the above oxytocics should be injected intravenously and repeated one time. If the bleeding continues, the uterus must be packed. A transfusion of 1,000 ml. or more of blood, if necessary, must be given at once. Periodic hemoglobin or hematocrit determinations must be made.

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TOXIC COMPLICATIONS OF PREGNANCY IN GORGAS HOSPITAL, PANAMA CANAL ZONE, 1931-1945*†

An Analysis of 10,000 Pregnancies

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REPORTS on pre-eclampsia and eclampsia under tropical conditions have been few and inconclusive. In the tropics of the Western Hemisphere the only reports available show Puerto Rico and Trinidad to have some of the highest rates in the world.[1] The records of Gorgas Hospital on the Isthmus of Panama afford an unusual opportunity to evaluate the influence of race and economic conditions as well as the effects of a tropical climate on pregnancies under good prenatal care.

The Canal Zone is not only similar in climate to Puerto Rico and Trinidad, but also has two racial groups, the "Panamanians" and the West Indian Negroes, respectively, who are comparable to the chief inhabitants of these two areas and might be expected to show the same high incidence of pre-eclampsia and eclampsia. A third distinct group, the white Americans, can also be studied in Panama and the incidence of their difficulties in pregnancy compared with reports for various parts of the United States. De Snoo[2] has reported that Europeans living in Batavia, Java, have nearly five times as much eclampsia as do the natives, and about three and one-half times as much as the Chinese living there. The incidence of pre-eclampsia and eclampsia in Americans in Panama was therefore of considerable interest.

Recent studies[3-7] have shown that the poorer nutrition of the lower economic groups may be an important factor in their generally high incidence of toxic complications during pregnancy. In Panama there are two distinct economic groups of Panamanians eligible for treatment in Gorgas Hospital. The larger of these is obliged to live on the low salary scale of the "silver" payroll. The Panamanians on the "gold" payroll receive the same relatively high wages as the Americans. This division of the employees of the Panama Canal into "silver" and "gold" is found throughout the administration of the Zone and dates back to the early construction days when laborers were paid in silver coin and the clerical and administrative workers were paid in gold. This study, because of these sharp economic distinctions, was able to investigate the role of nutrition and hygiene in the incidence of the toxemias of pregnancy in Panama.

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Various authors have noted seasonal changes in the incidence of eclampsia in many parts of the world. It has been associated with cool rainy weather,[8] cool dry weather,[9] high humidity,[10] high temperatures,[11] warm moist weather,[12] and changeable weather.[13, 14] Scheyer[15] is unable to establish any correlation with the weather. In Panama, the temperature is remarkably uniform, but the year is divided into a rainy season and a dry season, the dry season is preceded in December and followed in May by a period of changeable weather. The rainy season extending through the second half of the year becomes progressively wetter, although there is generally considerable sunshine and clear weather each day. The possible effect of these seasonal changes on the occurrence of the toxic complications of pregnancy was investigated.

Hypertension is generally considered to be less common in the tropics. Thonnard-Neumann[16] and Kean[17, 18] have found that while this is true for the native Indian and Panamanian, the Negroes show a very high incidence of hypertension beginning at an early age. The relation of this hypertensive tendency in the Negroes to the incidence of the transient hypertension of pre-eclampsia was examined.

The present investigation studies these and related problems by an analysis of the more than 10,000 patients delivered in Gorgas Hospital in the years 1931 to 1945. The clinic and hospital record of every patient was studied, and the diagnosis made or checked by the senior author in accordance with the criteria to be described. Differences in diagnostic standards during these years do not enter appreciably into the final tabulations. We have endeavored to describe the distribution of the toxic complications of pregnancy in the population studied, although we cannot with any certainty account for many of the characteristics of this distribution. This survey was planned as a basis for further study of possible causative factors in "toxemias."

Material and Methods

The Patients.—The division of employees of the Panama Canal into "silver" and "gold" has already been noted. The Health Department also operates on this basis. In the "*silver*" clinics, dispensaries, and wards are seen all of the West Indian Negroes and a large proportion of the Panamanians. Their income is sharply limited by low fixed standards, housing is crowded, families are large, and life for them is a continuous economic struggle. The "*gold*" patients, who are largely Americans, have the advantage of premium wages, low tax free prices at Government Commissary or Post Exchanges, and generally spacious accommodations. The standards of medical care for these two groups are essentially the same. All doctors are on a full-time salary basis, and no fees are charged for their medical services. Although the hospital charges are minimal, they are frequently a difficult burden for the low income patients.

The West Indian Negroes by appearance, background, customs and language constitute a sharply defined group. Only patients who were born in Jamaica, the Barbados, or other West Indian islands, or whose parents were born there are classified in this group in the present study. In a few more years this classification will break down as present "West Indian" children born in Panama mature. Thousands of these Negroes have been imported as laborers since the early days of the canal. Social and political barriers to intermarriage with the "Pamanians" are often broken, and many patients in our series are really mixtures of these two strains. Such patients are included with the

"Panamanians" in this study. In the preliminary tabulations a group of patients who could be identified as Spanish and Indian mixtures with little or no Negro ancestry were studied separately from the remainder of the silver "Panamanian" group. However, such differences as were found could not be considered significant, and this separation does not appear in the tables presented.

The original Panamanian was an Indian. To his stock for 300 years has been added the blood of Europeans, particularly Spanish, and of an indeterminate number of Chinese, Hindus, Negroes, and people of other "races." The Panamanians on the gold pay roll included very few recent European-Panamanian mixtures. Individuals with one or more recent Negro antecedents were somewhat more frequent among the Panamanians on the silver pay roll.

The Americans have come from all parts of the United States and remain for a varying length of time; some for only a year, but many spend the rest of their lives in the Canal Zone. They represent a fair cross-section of the white citizens of the United States in their racial makeup. Their economic status in the Zone is uniformly very good.

The Records.—In the *silver* clinic the prenatal records were kept chronologically in bound volumes with a page for each patient. In the *gold* clinic the same information was kept for each patient on combined obstetric and surgical history cards. During most of the fifteen-year period these clinics were under the personal direction of one man (Dr. Howard K. Tuttle). During his vacations and following his retirement in 1945 the same procedure was followed.

Blood pressures were determined at each visit by the auscultatory method using a mercury sphygmomanometer. Urine specimens were filtered and tested for albumin by layering over nitric acid. A distinct ring of precipitate was read as positive. All clinics were held in the afternoon.

Every clinic record was examined. A patient whose course suggested a prenatal irregularity or who was signed out of the hospital with any abnormality of pregnancy was carefully investigated. The final diagnosis was made with the aid of the combined clinic and hospital records. Only cases actually delivering in Gorgas Hospital were included in the final tabulation.

The total number of births and stillbirths was obtained directly from the official register of births for Gorgas Hospital. In order to learn the total number of pregnancies in each racial group, 1,243 records were examined (approximately every tenth delivery), and the patient was classified as to race in the same manner as was done for all the abnormal patients studied. The percentage of the total number belonging to each group was calculated from these figures and applied to give the group totals. The delivery records of each of the 343 stillbirths were similarly examined for racial classification.

Criteria for Diagnosis.—Any patient with a previously normal blood pressure range who showed a distinct rise of 20 mm. of Hg or more in diastolic to a blood pressure of 140/90 or higher with or without albuminuria, edema, or other signs was considered abnormal. If adequate evidence was at hand that this rise was of more than transient nature, i.e., if despite bed rest and oral magnesium sulfate, it persisted for several days in an outpatient or for several hours in a hospitalized patient, then pre-eclampsia was diagnosed. If the pressure rose and remained above 150/100 for some period of time and if there was present marked albuminuria, edema, and/or subjective symptoms of severe headache, visual disturbances, abdominal pain, dizziness, etc., the condition was diagnosed as severe pre-eclampsia.

A small percentage of cases was included as pre-eclampsia which did not meet fully the above blood pressure requirement. In these cases severe albuminuria, marked subjective symptoms, or initial hypotension seemed to

justify the diagnosis. Eclampsia was diagnosed in patients with no previous history of convulsion who had one or more convulsions, witnessed by a staff member, at or near term. Most of the eclampsia cases had all of the findings of the severe pre-eclampsia group in addition to their convulsions. Convulsions occurred within twenty-four hours after delivery in the cases diagnosed as post-partum eclampsia. Persistent severe albuminuria without hypertension was listed simply as albuminuria of pregnancy. Transient mild albuminuria detected in clinic was found to be very common and is discussed separately.

The maximum rise in blood pressure was determined by taking the first or second clinic blood pressure recorded, whichever was lower,* and comparing it with the highest diastolic recorded. The highest systolic blood pressure in the tabulation is in every case that accompanying the highest diastolic and is not necessarily the highest recorded. In a few cases blood pressures taken before the toxemia developed were not available and the highest diastolic blood pressure was compared with the blood pressures post partum, if these were in the normal range.

Patients were considered to have hypertension antedating their pregnancy if (a) hypertension was present on previous admissions to the hospital unassociated with a possible toxemia, or (b) hypertension was present at several successive clinic visits, the first of which occurred before the last trimester, and the hypertension persisted after delivery. Blood pressures consistently above 140/90 were considered evidence of hypertension, and in most cases these patients showed frequent blood pressures in the range of 150/100 or above. If the symptoms of their hypertension became definitely worse during the last trimester of pregnancy (usually involving a rise of 20 or more points in diastolic pressure over the previous diastolic pressure range) the patient was judged to have signs of pre-eclampsia superimposed on their initial hypertension. In most cases there was also an increase in albuminuria, edema, and subjective symptoms.

The grading and observing of edema was dependent on the judgment of the individual physician. Therefore, although its presence or absence is noted in our report, failure to find it recorded for a patient did not necessarily mean that it was never present. Similarly it was recognized that subjective symptoms were not recorded with equal care in all records. Fortunately, the blood pressure was always taken and the urine examined at each visit. Within the limits of the accuracy of their measurement, these signs could be depended upon for diagnosis and comparison. Due to contamination with the lochia, uncatheterized urine findings were not considered after delivery.

Results

Table I summarizes the main incidence data obtained. It will be seen that the Americans show a relatively low incidence of pre-eclampsia and that most of the cases are mild. While the pre-eclampsia rate for the Negro population is more than twice that for the Americans, it is no higher than the rate reported for many cities in the United States and is far below the rates cited for Trinidad and Puerto Rico. Similarly the incidence of eclampsia in Negroes, while nearly eight times the very low rate for Americans, is not unusually high by United States standards.[1] A relatively high incidence of hypertensive disease antedating pregnancy was found in the West Indian group. The superior economic status of the Panamanians on the gold pay roll was not reflected in the incidence data. Although the incidence of pre-eclampsia in this group appears to be lower than that of the silver roll Panamanians, they show the highest incidence of eclampsia.

*It was noted that the first recorded blood pressure was often considerably higher than subsequent ones, due presumably to the excitement of a first visit.

TABLE I. INCIDENCE OF MAJOR TOXIC COMPLICATIONS OF PREGNANCY IN GORGAS HOSPITAL, 1931 TO 1945*

	GOLD ROLL (HIGH INCOME)				SILVER ROLL (LOW INCOME)			
	AMERICAN		PANAMANIAN		PANAMANIAN		WEST INDIAN	
TOTAL DELIVERIES†	2,052		935		2,123		5,050	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Mild pre-eclampsia	70	3.4	26	2.8	82	3.8	313	6.2
Severe pre-eclampsia	13	0.6	11	1.2	29	1.4	93	1.9
Ante- and intrapartum eclampsia	1	0.05	9	0.96	10	0.47	23‡	0.46
Postpartum eclampsia	1	0.05	2	0.21	5	0.24	9	0.21
Hypertension with superimposed pre-eclampsia	6	0.3	0	0	15	0.7	48	0.9
Hypertension apparently uninfluenced by pregnancy	2	0.1	5	0.5	8	0.4	47	0.9
Therapeutic abortion for hypertension§	1	–	0	–	1	–	7	–
Albuminuria	3	0.15	0	0	13	0.6	20	0.4

*One silver and four gold patients with definite hypertension but with inadequate data recorded in their clinical records to show the nature of this hypertension are not included in this table.

†Based on a racial sampling of 1,236 patients which yielded: 225 Americans, 116 Gold Panamanians, 264 Silver Panamanians, and 628 West Indians.

‡Since these are not included in the total patients beyond the fifth month of gestation delivering in hospital, the percentage incidence cannot be calculated.

§Includes four hypertensives with superimposed eclampsia.

TABLE II. THE PROBABILITY OF SIGNIFICANT DIFFERENCES BETWEEN GROUPS*

	GOLD VS. SILVER		AMERICAN VS. GOLD PANAMANIAN		SILVER PANAMANIAN VS. WEST INDIANS		GOLD PANAMANIAN VS. SILVER PANAMANIAN		
									LIABILITY‡
	χ^2†	P	χ^2	P	χ^2	P	χ^2	P	P
1. Mild pre-eclampsia	18	*<.0001*	.5	.5	11	*.001*	1	.3	.1
2. Severe pre-eclampsia	11	*.001*	2	.2	2	.2	.1	.9	.1
3. Eclampsia	3	*.08*	12	*.001*	.1	.9	1	.3	*.04*
4. Hypertension	23	*<.0001*	.1	.9	5	*.020*	1.6	.2	*.015*
5. Albuminuria	6	.015	Binomial§	.3	1	.3	Binomial§	*<.001*	.7

*Certain of the categories of Table I have been combined for statistical analysis. "Significant" probabilities are italicized.

†χ^2 for Gold vs. Silver and for other comparisons has 1 d. of f. as calculated from a 2 x 2 contingency table using Yates Correction.

‡Liability is the probability of concluding "not significant" when a discrepancy exists between Panamanians as large as that between Americans and Negroes.

§The exact Binomial is used where frequencies are small.

It seemed reasonable to draw conclusions from a detailed study of more than 10,000 cases covering a period of fifteen years. Nevertheless, it must be recognized that in disease groups with small numbers, sampling errors are large. It is important to know which difference in incidence may be accepted with confidence and which may possibly be due to sampling errors. Accordingly the data were subjected to rigorous statistical analysis. Some of the statistical evaluations are listed in Table II.

The data have been so grouped that in general two main factors are operating in the categories of Tables I and II: One economic (including dietary) and the other racial.* The greatest differences in incidence occur between the

*The extent to which psychological factors may be concerned is considered in the discussion.

American and West Indian groups, and one would like to be able to attribute these differences to *either* of these two factors or to *both* in known proportions. However, the importance of economic factors can be tested only by comparing the two "Panamanian" groups. Furthermore, an insignificant result does not necessarily mean that economic factors are not important. It may mean only that the number of cases is insufficient to detect a difference. In some categories large differences in the "supply" could exist, and yet the statistical conclusion from the sample studied would be "no difference." The *liability* of making a false conclusion of "no difference" when a difference exists as large as that between Americans and West Indians is given in the last column of Table II. Similarly, racial factors can be tested only within the gold or within the silver groups, and the same precautions must be observed in interpreting the results.

In every category the Negroes had a significantly higher incidence of disease than did the Americans. Even when the gold versus silver differences are compared in Table II, they are found to be highly significant (except for eclampsia). Within the gold group, the high income Panamanians had essentially the same incidence of pre-eclampsia as the Americans, but they did have significantly more eclampsia. The Negroes have significantly more pre-eclampsia than do any of the other groups.

When the high and low income Panamanians are compared, there is no statistical basis for concluding that there is a difference in the incidence of either pre-eclampsia or eclampsia in these two groups. To conclude that there is not any difference in pre-eclampsia in these two groups is to run a 10 per cent chance of being wrong (Liability 0.1). A difference in the incidence of eclampsia as great as that between the Americans and West Indians would have been detected (Liability 0.04).

Patients With Hypertension Antedating Pregnancy.—The significantly higher incidence of hypertension in the silver patients as compared with the gold is beyond doubt. The higher incidence of hypertension in the West Indian Negroes than in the Panamanians also seems well established. Within the Panamanian groups, the incidence of hypertension in the low and high income groups could not be shown to differ significantly.

Of the 135 cases of pregnancy hypertension in which the pregnancy continued beyond the fifth month, 55 per cent showed the development of signs of superimposed pre-eclampsia. The great majority of these cases were in Negroes. Fifty per cent of the hypertensive Negroes developed pre-eclampsia, and 4 per cent had actual eclamptic convulsions. Arnell[19] and Dexter and Weiss[20, 21] report similar findings. The high incidence of abortions and stillbirths in obstetric patients with hypertension despite a good prognosis for the mother has been repeatedly emphasized.[22-24]* This is confirmed by Table III in which it will be noted that the fetal mortality remained 12 to 13 per cent whether or not toxemia developed. There were no maternal deaths of patients with essential hypertension in this series. To the fetal deaths due to hypertension listed in Table IV must be added the 10 therapeutic abortions for hypertension noted in this series and many spontaneous abortions not recognized or recorded as associated with this condition.

Blood Pressure.—The blood pressures associated with the complications enumerated above have been analyzed and their distribution noted. The average rise in diastolic blood pressure in pre-eclampsias classified as mild was 27 mm. of

*On the contrary Sharkey and Hess[25] find no adverse effect of maternal essential hypertension on the child, when the incidence of abortions, premature births, stillbirths, and neonatal deaths was compared in 115 patients with essential hypertension and 2,885 without. Barnes and Browne[23] cite excellent evidence to show that pregnancy has no effect on the mean level of blood pressure or the incidence of hypertension at any age. They conclude that pregnancy does not cause a latent tendency to hypertension or have an adverse effect on a mother with hypertension. Furthermore, they fail to find any *permanent* vascular damage associated with toxemia, although the renal damage may take up to two years to heal completely. They report, however, that hypertension in the mother does increase the risk of losing the baby.

TABLE III. FETAL AND MATERNAL MORTALITY ASSOCIATED WITH TOXEMIAS

	TOTAL CASES	NUMBER OF STILLBIRTHS AND NEONATAL DEATHS*	PER CENT	MATERNAL DEATHS	PER CENT
Mild pre-eclampsia	491	20	4.1	0	-
Severe pre-eclampsia	146	28	19.4	4	2.7
Ante- and intrapartum eclampsia	47	12	25.5	10	21.3
Postpartum eclampsia	17	1	5.9	3	17.7
Hypertension and pre-eclampsia	66	8	12.1	0	-
Hypertension	60	8	13.3	0	-
Persistent albuminuria	36	2	5.5	0	-
Totals	863	79	9.2	17	2.0

*Includes only deaths up to approximately 1 week after delivery.

Hg ($\sigma = 9$). In the severe pre-eclamptic group it was 42 ($\sigma = 11$) and in the eclamptic patients 39 mm. of Hg ($\sigma = 12$).

It is noteworthy that in 15 per cent of the patients diagnosed as having eclampsia the highest diastolic pressure recorded was below 90 mm. of Hg compared with 2.0 per cent below this figure in the mild pre-eclampsia group and 0.7 per cent (one patient) in the severe category. It is apparent that there was a small group of eclampsia patients with definite convulsions and other symptoms, but whose blood pressure was not markedly elevated at any time that it was determined in the hospital or clinic.

In those patients with prepregnancy hypertension who developed superimposed toxemia, the average rise in diastolic pressure was 41 mm. of Hg ($\sigma = 12$) for the 18 cases considered severe, and 25 ($\sigma = 11$) for the 51 considered mild. The highest diastolic pressures averaged 133 ($\sigma = 12$) and 118 ($\sigma = 11$), respectively, in the severe and mild groups with accompanying average systolic blood pressures of 200 ($\sigma = 18$) and 180 ($\sigma = 20$).

Albuminuria.—The presence of albuminuria was noted before delivery in 93 per cent of the eclamptic and severe pre-eclamptic patients, but only 60 per cent of the mild pre-eclamptics showed this symptom. In all of these cases the urine was tested several times in the clinic and in the hospital. Cases in which the severity of the other symptoms left no doubt as to the diagnosis often failed to show albumin in the urine.

A high percentage of silver clinic patients showed albumin in their urine at some time or other during the prenatal period. During 1936 to 1940 albuminuria was found in 34 per cent of the silver clinic patients, and during 1941 to 1945 in 21 per cent.

It should be remembered in comparing figures from different clinics that the actual percentage of patients showing albuminuria in clinic is in part a function of the number of clinic visits. About 15 per cent of those visiting clinic only once during 1936 to 1945 showed albuminuria, compared with 20 per cent for those seen twice, 28 per cent after four visits, 36 per cent after six, and 45 per cent after 10 or more visits. The average number of clinic visits of all silver patients seen was 4.5.* The gold clinic incidence of transient albuminuria was strikingly lower than that of the silver clinic, averaging 9 per cent over the fifteen-year period. The techniques employed were the same, except for the fact that the gold clinic patients brought urine specimens with them in most cases.

*Many of the patients seen only once or twice proved ineligible for clinic treatment and were not followed through the remainder of their pregnancy. Thus the average number of clinic visits for patients in our main study series, all of whom delivered in the hospital, is much higher.

Edema.—The common occurrence of edema in pregnant women without other toxic signs has been stressed by Dexter and Weiss,[20] Dieckmann,[1] and others. In our series, a number of patients were hospitalized for massive edema, yet showed no albuminuria or hypertension. Nevertheless, 76 per cent of the eclamptic and severe pre-eclamptic patients, and 57 per cent of the mild pre-eclamptics were noted to show either dependent or generalized edema. However, the occurrence of mild edema may not have been recorded in some cases.

Subjective Symptoms.—The recording and interpretation of subjective symptoms, particularly of headache, was so variable that no attempt was made to analyze them. Their presence was taken into consideration in judging the classification of borderline cases.

Time of Onset.—Nearly half of the ante- and intrapartum eclampsias began in the thirty-fifth to the thirty-seventh week. Eighteen per cent of the total number began before the thirtieth week. One of the postpartum eclampsias followed a premature delivery at twenty-eight weeks, the other cases were in patients delivering at or near term.

The onset of the cases of mild pre-eclampsia showed a symmetrical distribution about a sharp peak at thirty-eight weeks. No cases occurred before the thirty-first week, and only 18 per cent of the cases occurred before the thirty-fifth week. In contrast 38 per cent of the severe cases of pre-eclampsia developed before the thirty-fifth week, and 10 per cent on or before the thirty-first week. The severe cases showed two broad peaks of onset, one at thirty-one to thirty-three weeks, and a second coinciding with the peak for mild cases around the thirty-seventh to thirty-ninth week. There was one patient whose symptoms were mild when they first appeared at forty weeks, but became severe following delivery.

The patients who developed pre-eclampsia in addition to their prepregnancy hypertension tended to do so earlier in pregnancy than the pre-eclampsia group as a whole. Furthermore, the more severe superimposed pre-eclampsias tended to begin earlier than the mild ones (average onset at 27.5 weeks, σ 5.6 as compared with 35 weeks, σ 4.5, for the mild).

While estimations of the date of onset are subject to considerable error because of the delay in seeing the physician, there seems to be a tendency in our series for the pre-eclampsias which develop earlier in the prenatal course to be more severe (cf. 26). The average onset of persistent severe albuminuria is thirty-one weeks ($\sigma = 9$) in this series, but the individual onsets range evenly from fourteen to forty-two weeks.

Age and Parity.—The many observations indicating a much higher incidence of toxemia in first pregnancies are supported by the present series. Eighty per cent of the eclampsias and 52 per cent of the pre-eclampsias were found in primiparous patients. The percentage of primiparous women seen in the silver clinic was 38 per cent. Records were not analyzed for the percentage seen in gold clinic or in the hospital.

Certain differences were noted in age incidence in the different diagnostic categories. The age incidence curve for mild pre-eclampsia followed the age distribution curve for normal pregnancies, but the severe pre-eclamptics showed two distinct incidence peaks. The first corresponded to the normal age peak for all pregnancies. The second peak occurred in the 33 to 35 year range following a period of low incidence from 27 to 29 years. The incidence of eclampsia showed this same double humped curve and differs only in the greater percentage of cases in the 14- to 23-year age range, and the somewhat later second peak (at age of 36 to 38 years). The existence of these departures from normal was confirmed by statistical tests.

The hypertensive pregnancies were symmetrically distributed about a sharp peak at the age of 30 to 32 years. Sixty-seven per cent of the hypertensives and 74 per cent of the hypertensives with superimposed pre-eclampsia were

over 33 years of age. The former averaged four previous pregnancies and the latter five. However, approximately 20 per cent of the patients falling in each hypertensive category were primigravidas.

Multiple Toxemias.—Only two Americans had more than one pregnancy complicated by toxemia, one with two mild pre-eclamptic episodes and one with hypertension on the first recorded pregnancy and mild pre-eclampsia superimposed on her hypertension in the second. Two gold Panamanians had two and three mild pre-eclampsias, respectively. A third had three pregnancies with hypertension and showed definite signs of chronic nephritis with the last two of these.

In contrast, 52 of the West Indians and 13 of the silver Panamanians had a total of 150 complicated pregnancies. Ten of the West Indians and two of the Panamanians had three such pregnancies, and four of the West Indians had four. Twenty-one of the Negroes and four of the Panamanians with more than one complicated pregnancy had pre-existing hypertension with one or more of these pregnancies. Fifty per cent of these patients developed their hypertension following one or more pregnancies with mild or severe pre-eclampsia alone.

So many combinations of diagnoses on successive pregnancies were encountered in the silver group that they could not be reduced to a common table. However, it may be noted that a severe pre-eclampsia followed a mild one in eight cases, a mild succeeded a severe in eight, and pre-eclampsia superimposed on hypertension occurred after a pregnancy with hypertension alone in four. In two successive pregnancies mild pre-eclampsias were noted in 23 cases, severe ones in six, and albuminurias in four.

Fetal and Maternal Mortality.—The fetal and early neonatal mortality associated with mild pre-eclampsia was 4.1 per cent in this series, and that with severe pre-eclampsia, nearly 20 per cent (Table III). In addition, there were four maternal deaths in the latter group. While the incidence of fetal deaths was much lower in postpartum eclampsia, due to prior delivery of the child, than in ante- and intrapartum eclampsia, the difference in maternal death rate is not significant. Eclampsia accounted for more than three-fourths of the maternal deaths in the group of complications of pregnancy studied. No maternal deaths occurred among the 106 hypertensive pregnancies, although 18 of these had an apparently severe pre-eclampsia superimposed. The fetal death rate in patients with hypertension was relatively high, but was not increased when pre-eclampsia was also present.

The total incidence of stillbirths is lowest among the Americans (Table IV). The higher percentage in the gold Panamanians is probably due in part to the higher incidence of eclampsia. The over-all stillbirth incidence was 3.4 per cent. Neonatal deaths were not tabulated in the hospital records except

TABLE IV. INCIDENCE OF STILLBIRTHS IN GORGAS HOSPITAL

		TOTAL STILLBIRTHS FROM ALL CAUSES*	PER CENT OF TOTAL BIRTHS	STILLBIRTHS AND NEONATAL DEATHS ASSOCIATED WITH "TOXEMIA"
Gold Roll	Americans	42	1.9	9
	Panamanians	25	2.8	10
Silver Roll	Panamanians	92	4.4	16
	West Indians	184	3.7	47
All Groups		343	3.4	82

*Figures for total neonatal deaths were not available. During 1939 to 1941 stillbirths made up only 54 per cent of the combined total of stillbirths and neonatal deaths.

for the years 1939 to 1941. During this three-year period there were 75 stillbirths and 63 neonatal deaths recorded. The over-all incidence of maternal deaths for the conditions investigated is 1.9 per cent of the total cases with toxic complications or 0.16 per cent of the total deliveries.

Other Complications.—Nephritis without hypertension was found in four patients, with hypertension alone in six and with pre-eclampsia alone in one. In eight cases of nephritis with hypertension, pre-eclampsia also developed and was severe in three of these. The highest incidence of nephritis occurred in the West Indian Negroes, a finding which has also been reported from autopsy studies in Panama.[27]

In one case a severe postpartum psychosis followed eclampsia and in two cases it developed without signs of a toxemia. Two patients were admitted antepartum in an anxiety state. Ten silver and two gold patients showed signs of polyneuritis in association with previous nausea and vomiting. Pyelitis was not investigated for 1941 to 1945, but occurred in ten silver and four gold patients during the preceding ten years.

There were 251 charts signed out with a diagnosis of "vomiting of pregnancy" or "hyperemesis gravidarum." Of these, six were considered to be cases of true pernicious vomiting, three of which proved fatal. The percentage of admissions for vomiting of pregnancy which could be attributed to Americans and high income Panamanians, rose from 29 per cent in 1931 to 1940 to 59 per cent during 1941 to 1945, although their proportion of total deliveries did not change.

Of 822 abortions between 1941 and 1945, 173 were in gold and 649 in silver patients. A reliable breakdown was not readily available for the 861 abortions between 1931 and 1940.

TABLE V. SEASONAL INCIDENCE

MONTH	CASES OF PRE-ECLAMPSIA IN 15 YR. F^o	CORRESPONDING TOTAL DELIVERIES IN 15 YR. BASE*	EXPECTED CASES IN 15 YR. F^c†	PRE-ECLAMPSIA (F^o, F^c)[a] FC	PRE-ECLAMPSIA χ_M[a]§	ECLAMPSIA χ_M[a]	STILLBIRTHS χ_M[a]
Jan.	54	830	52	0.1	0.1	1.8	0.1
Feb.	38	800	50	2.9	3.2	0.8	0.1
March	41	770	48	1.0	1.1	0.8	0.1
Apr.	38	770	48	2.1	2.3	0.0	1.3
May	41	780	49	1.3	1.4	0.2	0.1
June	65	810	51	3.8	4.2	0.7	0.4
July	64	850	53	2.3	2.5	3.2	2.4
Aug.	52	892	54	0.1	0.1	0.7	0.3
Sept.	48	920	58	1.7	1.9	0.2	0.0
Oct.	67	930	59	1.2	1.3	0.2	0.3
Nov.	67	920	58	1.4	1.5	0.2	0.8
Dec.	61	890	56	0.5	0.6	0.7	3.9
Total	636	10,160	636	18.4‡			

*Base is the total number pregnancies taken from a smoothed curve corresponding to the total number of cases of pre-eclampsia. For pre-eclampsia and eclampsia it is estimated from the total number of deliveries a month later. For stillbirths base is estimated from the total number of deliveries two weeks later. This time lag is an arbitrary but reasonable assumption. The actual time lag is not critical in the statistical analysis. The complete table for pre-eclampsia is given as an example of the method employed.

†Expected cases: $fc = \frac{\text{Base}}{10{,}160} \times 636.$

‡For the total test, $\chi_t^2 = 18.4$ with 11 degrees of freedom which has a probability, $p = 7$ per cent of a χ_t^2 as large or larger than the one found. The $\chi_t^2 = 9.5$ for eclampsia and has a probability of 60 per cent. The χ_t^2 for stillbirths is 10.7 and has a probability of 50 per cent. From these probabilities it is concluded that all of the seasonal variations observed in the above conditions can be accounted for by random sample variation.

§For individual months, $\chi_M^2 = \frac{(fo-fc)^2}{fc}(1 + 1/12)$. This correction is necessary because each month has one degree of freedom. The value of χ_M^2 for a probability of 5 per cent is 3.7. Only the June pre-eclampsias and the December stillbirths reach this value.

Seasonal Incidence Changes

One of the principal points of interest in the present investigation is the influence of a tropical climate on a pathologic condition believed to fluctuate with the seasonal changes of the temperate zone. The results depicted in Fig. 1 show an apparent fluctuation in pre-eclampsia and vomiting with seasonal changes. However, this is probably deceptive and well illustrates the danger of drawing conclusions as to seasonal incidence without proper controls and statistical analysis of the data. Only the points indicated by solid circles in Fig. 1 represent significant monthly variations. The basis for calculation of significance and the actual chi square values are given in Table V. It is concluded that *no definite seasonal variation in the incidence of these toxic com-*

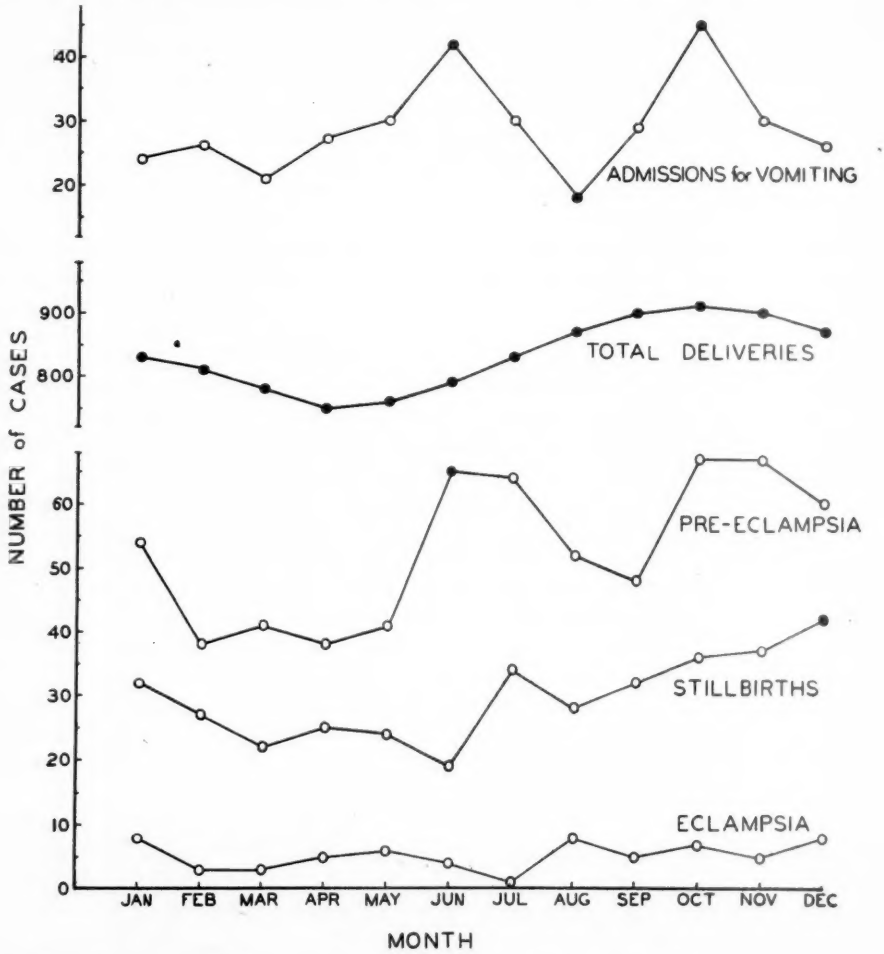

Fig. 1.—Seasonal variations in obstetric patients. The month of onset of pre-eclampsia and eclampsia and the month in which a stillbirth occurred were investigated by examining individual hospital and clinic records. The total deliveries occurring in each month from 1931 to 1945 are also plotted. The admissions for "vomiting of pregnancy" were tabulated from hospital records without verification of individual cases or correcting for repeat admissions. The seasonal variation in total births is not questioned. Those seasonal variations in incidence which are not accounted for by the seasonal variation in total pregnancies with a probability of 5 per cent or greater are represented by solid circles. The statistical data are given in Table VII.

plications of pregnancy in Panama exists in our figures for the fifteen-year period when the seasonal fluctuations in total births and the errors inherent in samples of the size studied are taken into consideration.

Annual Incidence Changes

For the two years following 1932, the incidence of pre-eclampsia remained below the figure of 4.75 per cent for this year (Fig. 2). In 1935 it rose sharply, but thereafter dropped steadily to approximately 4.5 per cent in 1938 and 1939. Since 1939 the pre-eclampsia rate has shown a continued upward trend except for a small drop in 1943. The incidence of pre-eclampsia doubled in the period from 1939 to 1945. The percentage increase was identical for both

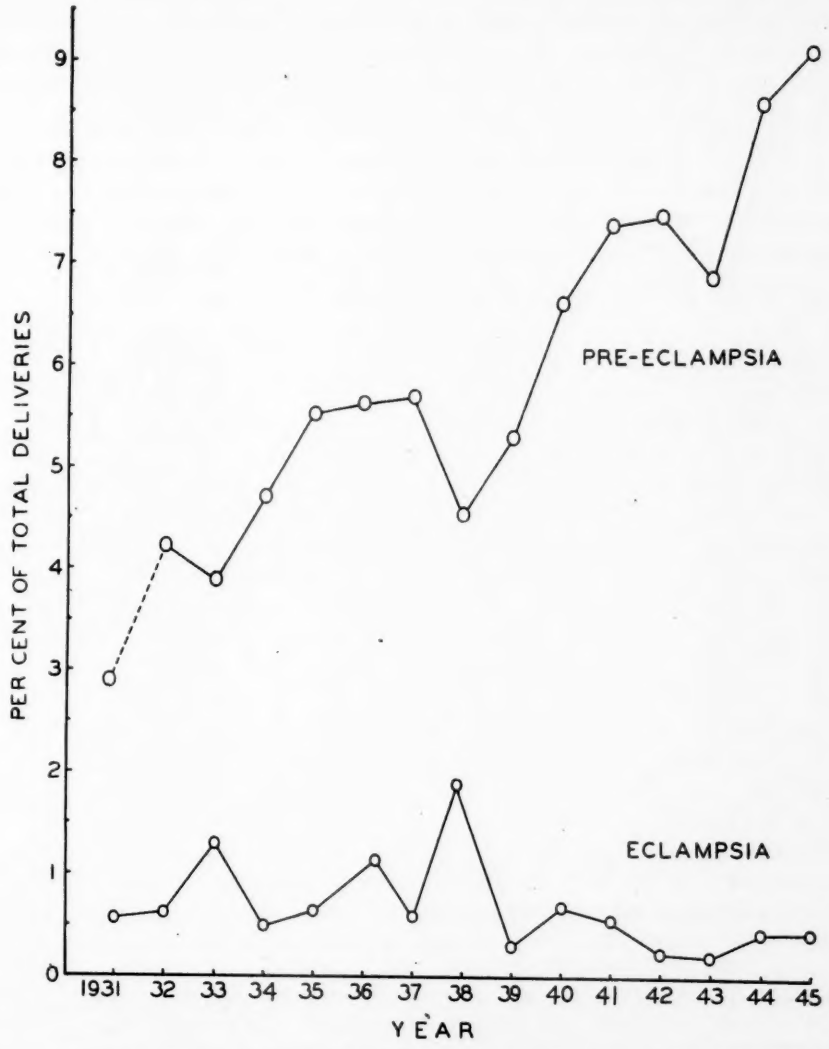

Fig. 2.—Annual incidence of pre-eclampsia and eclampsia. The value for 1931 is represented by a dotted line because the clinic records, although begun in the fall of 1930 might not be as complete for the cases delivering in early 1931 as for later years. It is hoped that the annual trends for other conditions of pregnancy can be presented in a later paper together with the inclusion of data for post-war years.

silver and gold groups. *Whatever factors made for this increase operated equally on diverse economic and racial groups.* In contrast to the pre-eclampsia rate, that for eclampsia showed sharp increases in eclampsia in 1933, 1936 and 1938. There have been no high incidence years since 1938 and the eclampsia rate has remained relatively low.

Factors of Possible Significance

The great variation in incidence of toxemia throughout the world, and even in different people in one locality, indicates that race, climate, economic status, diet, personal habits, social status, psychological stresses, and type of medical care must all be considered as factors of possible importance.

Race.—Whitacre and co-workers[28] compared eclampsia in Chinese in Peiping and Negroes in Memphis without observing racial differences. In New Orleans the incidence of pre-eclampsia and eclampsia has been reported to be the same in Negroes and white.[19, 20, 30] In Panama the Negroes show a much higher incidence of the various forms of toxemia than the white Americans. If this were entirely attributal to a racial susceptibility on the part of the Negroes, then such a lowered resistance should be apparent in New Orleans. Thus it would appear that the difference in incidence of pre-eclampsia and eclampsia in this study cannot be attributed to racial factors alone.

A similar conclusion appears justified for the incidence of hypertension, although there is little doubt that the Negro in the United States has proportionately more hypertension than the whites.[31-37] The present study as well as reports of Thonnard-Neumann[16] and Kean[18] show the Negroes to have a higher hypertension rate in Panama. It might be postulated that a racial susceptibility to essential hypertension exists in the Negroes and is paralleled, under similar conditions, by a lower resistance to the transient hypertension of pre-eclampsia and eclampsia. That this is not the complete answer is indicated by the absence of hypertension in most African Negroes. These reports include the Gold Coast Colony (Odaley[38]); Northern Rhodesia (Dry[38]); Southern Rhodesia (Waekford[38]); American Zulu Mission (Taylor[38]); Liberia (Shattuck[39]); East Africa (Dennison[40, 41]); Kenya (Jex-Blak[42]); and Congo (DuBois[42]). One must then assume the relative absence of factors precipitating hypertension in their native environment or doubt the true genetic basis for the increased hypertension in the Negro of the Western Hemisphere or both. The report that Negroes working in the city of Johannesburg, South Africa[42] do not appear to show such a complete immunity to hypertensive cardiovascular disease is evidence for the former.

Several authors have noted a much higher incidence of hypertension[16-18] and nephritis[44] in the West Indian Negroes as compared with the Panamanians. Yet these people appear to live under the same economic conditions and to have essentially the same diet.[45] It is not possible to conclude, however, that the differences noted between the Negroes and Panamanians in this and other studies in Panama are entirely racial. The Negroes as foreigners may be subject to greater stress in their adopted environment. *However, the fact that all Panamanians, gold and silver, seem to have somewhat less hypertension and pre-eclampsia, regardless of economic circumstances and environment, suggests that they may have some relative resistance to this condition on a genetic basis.* Whether this takes the form of a better adaptation to the climate, lower nutri-

tional requirements, greater neurovascular stability, greater endocrine stability or some other constitutional difference is not known.

Diet and Economic Conditions.—Differences in incidence of toxic complications exist within the silver group between the silver Panamanians and the West Indians. However there is no evidence that sufficient differences in sanitation, living conditions, income, diet or medical care exist to account for this. Furthermore, if these factors were sufficiently important to produce differences in incidence between low income groups, they might certainly be expected to affect the high and low income Panamanian groups where differences in diet and living conditions are marked.

Nevertheless, other studies[3-7] have clearly indicated the probable importance of nutrition in the incidence of "toxemias." Recently Dieckmann and associates[46] and Theobald[47] have reviewed this evidence and stressed the importance of further nutritional studies. Diet may have a relatively greater influence on the incidence of toxemia in circumstances different from those found in Gorgas Hospital patients. *We can conclude only that diet alone is not at present the limiting or determining factor in the incidence of pre-eclampsia and eclampsia in Panama. If a simple relationship between low incomes, poor diet, inferior living conditions, and a high toxemia incidence existed in Panama, there is probability of approximately 90 per cent that an analysis of our data would have indicated it.**

Climate.—The very high incidence of pre-eclampsia and eclampsia reported from Puerto Rico and Trinidad suggests that, on the basis of climate alone, the incidence of these diseases in Panama might be high. On the contrary, it is relatively low. Americans coming to the tropical climate of the Canal Zone run a lower statistical risk of "toxemia" than those in most parts of the United States. Similarly their incidence of hypertension is low. This observation is in accord with the widespread idea that circulatory stress and strain and actual hypertensive disease are less frequent and less severe in tropical climates.[48, 55] Nevertheless, one group, the West Indian Negroes, continues to show a high incidence of hypertension in this environment. Thus a warm equitable climate alone is not sufficient to insure a low rate of hypertension, nor is it necessarily associated with a high rate of toxemia.

Although the gross monthly figures for *pre-eclampsia* incidence in this study suggest some seasonal variation, these do not reach a 5 per cent level of significance by the statistical criteria adopted. There is no evidence in our series of significant seasonal variations in *eclampsia.* Some of the many contradictory reports of correlations of eclampsia with seasonal weather changes have been cited.[8-15] *It is suggested that the reason for the serious discrepancies reported in the literature is the tendency to suggest seasonal variations on admittedly inadequate data, the failure to consider seasonal variations in total deliveries, and the neglect of an adequate statistical analysis.* Sapeika[56] has recently come to similar conclusions. Jaffe's[57] idea that hypertension in Chicago Negroes is associated with the severe climatic stress of storm tracts to which they are not biologically adapted is untenable in view of the reports from Panama where the climatic stress is extremely low.[58]

Psychological and Social Factors.—Hypertension is rare in Negroes in Africa but common in Negroes of the western hemisphere on a wide range of diets. Many authors have called attention to the fact that hypertension is a disease of occidental civilization.[59, 60] There is evidence that the inability to ac-

*The experiences of Burke et al.[5] indicate that the differences in the incidence of complications of pregnancy in excellent diet groups as compared to good and fair ones are not great. Only when the diet is poor or very poor can its adverse influence be readily detected. Although the diet of the low income patients was found to be grossly inferior to those on the higher income status of the gold payroll,[45] it is not as poor as commonly found in many clinic patients in Rochester (Scrimshaw, unpublished data) or other cities in the United States.[3-5] This might account for our failure to find dietary factors of importance in this study.

cept or satisfy either passive wishes or hostile impulses may be a provoking factor in essential hypertension.[61-65] It is most suggestive that the Negroes in Panama, an unassimilated and unsatisfied group confronted with greater social problems than the Panamanians, have a higher incidence of hypertensive disorders.

Gastric ulcer, another disease associated with civilization and nervous factors, has been reported to occur twice as frequently in the West Indian Negro laborer as in the native Panamanians or the Americans in the Canal Zone.[66, 67] In contrast stands the very low incidence of peptic ulcer in Negroes in Johannesburg, South Africa hospitals.[68, 69] The higher admission rate of Negroes in the United States to mental institutions has been attributed to the greater economic and social problems with which the Negro must struggle.[70-72] More psychosis associated with disease has been reported in the West Indian women in Panama than in any other group.[73]

Schwab[74] has reported quantitative differences in the Negro in reaction to standard vasomotor stimuli. It is possible that the increased psychological stress incident to discrimination and to adjustment to a new situation, with or without accompanying relative racial susceptibility to neuro-vascular pathology, may have considerable influence on the incidence of both essential hypertension and pre-eclampsia in the Negroes of Panama.

Medical Care and Patient Cooperation.—Throughout the discussion it has been necessary to exclude the eclampsia rate in the gold Panamanians from the generalizations. The medical care of all the groups was essentially the same, but a few of the privileged Panamanians were decidedly uncooperative. They did not report regularly nor follow the instructions of the physician and may have unduly contributed to the small group of gold eclampsia cases. The hospital may also have accepted ineligible patients with eclampsia to the gold service through diplomatic channels when an exception would not have been made for a potential silver patient who was not entitled to Gorgas Hospital privileges. These factors cannot be evaluated a posteriori, and no conclusions as to higher incidence should be based on only 11 patients in fifteen years.

The failure of the eclampsia rate to rise during the war years as did the pre-eclampsia rate must be attributed in part to the practice of hospitalizing patients at the earliest signs of toxemia. Eclampsia was very rare in patients who reported regularly to clinic. The incidence rates given in this report do not apply to the majority of the inhabitants of Panama City, for these persons do not receive comparable prenatal care.

General Comment

Many local considerations cannot be described in detail in this report. For example, there has been considerable prejudice at times against the West Indians on the part of the Panamanians, and at one time they were refused Panamanian citizenship. On the other hand large numbers of the Negroes live in government communities within the Canal Zone where their living conditions are somewhat better than those of Panamanians and Negroes living in Panama City. The interplay of these and other local influences is hard to evaluate. In the introduction and discussion an attempt has been made to take these factors into consideration although they are not always specifically described.

The recent increase in the incidence of pre-eclampsia is of considerable interest. Since it is a proportionate increase in both gold and silver women, it would seem to reflect a response to changed conditions or cyclic influences com-

mon to both groups. The increase is a real one and not due to changed standards of medical diagnosis. No explanation of this rise is attempted at the present time, but the future trend will be followed.

Summary

The occurrence of toxic complications of pregnancy in 10,160 deliveries in Gorgas Hospital, Panama Canal Zone, in the period from 1931 to 1945 has been investigated. The incidence of pre-eclampsia, eclampsia, hypertension ante-dating pregnancy, hypertension with superimposed pre-eclampsia, albuminuria, and stillbirths is discussed in detail for the four main population groups. These include the Americans, the high income Panamanians, the low income Panamanians, and the West Indian Negroes—also a low income group. In general, the incidence of toxic complications is low in the Americans and highest in the West Indians. The annual incidence of pre-eclampsia has increased steadily since 1939. No significant seasonal variations could be found. The higher incidence in Negroes in Panama cannot be adequately accounted for by racial, dietary, therapeutic or climatic factors. It is concluded that adverse social and psychological factors affecting the Negroes to a greater degree than the other population groups may be an important influence.

The authors greatly appreciate the cooperation received from the staff of Gorgas Hospital and particularly Dr. William Coppinger, in charge of silver obstetrics and gynecology and Dr. Arthur N. Springall, assistant to the superintendent. Miss Martha Thomason greatly assisted in the tabulation of the data as did also Miss Katheryn Harrington, Dr. Robert Bays, and Dr. Roy Greer. Gratitude is also expressed to the file room staff who cheerfully located and relocated the thousands of hospital records required for this study.

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FURTHER OBSERVATIONS ON THE USE OF THE NEUTRAL DIET AND HYDRATION IN THE TREATMENT OF TOXEMIAS OF LATE PREGNANCY

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THE toxemias of pregnancy have long constituted a field presenting many new trends of thought and research. With current investigators constantly expanding the available data, it is not possible to condense all the information into a static picture. The literature has grown logarithmically with time, and even a bibliography on the subject would fill volumes.

Toxemia of pregnancy has always been one of the three major causes of maternal death. At present, with the advent of satisfactory sulfonamides and penicillin to combat infection, and with improved methods of collecting, storing, and administering blood and blood products, it may be safe to prophesy that pregnancy toxemia may come to rank first among the causes of maternal death.

All methods of treating the toxemias of pregnancy are designed to lower the mortality figure in this all-important death producing "disease" which is associated with or results from the pregnant state. Even though no one etiologic concept explains all the findings in pregnancy toxemia, management today resolves itself into the treatment of the signs and symptoms of a pathologic complex found only in pregnant individuals who were otherwise normal in the nonpregnant state. Regardless of the cause, the pregnancy toxemia patient presents certain manifestations which must be treated when they occur, or which must be prevented from presenting themselves at all, if possible.

Since Jan. 1, 1935, a uniform method of medical management of all patients with toxemia of pregnancy has been employed at the University of Michigan Hospital, as earlier reported.[1] All such patients have been treated according to an established conservative regime, modified to treat the individual case. In order to further evaluate this method of treatment, the records of 224 patients with pregnancy toxemia were reviewed.

The age variation was from 15 to 44 years, with 116 patients (52.2 per cent) below the age of 24 years, which is in accord with the general observation that toxemia is an affliction of young gravida. Fourteen patients (6.3 per cent) were 40 years of age or older; it is interesting to note that multiparity, hypertension, and renal disease were common to this older age group. Of the entire group of patients, 119 (53.5 per cent) were primigravidas, another observation characteristic in toxemia of pregnancy. One hundred ninety-eight patients were white; 26 (11.6 per cent) were Negroes, one of whom developed eclampsia.

Classification

These patients were classified according to the classification prepared by the American Committee on Maternal Welfare. The distribution of the various types is set forth in Table I.

TABLE I. TYPE OF TOXEMIA

TYPE	NUMBER	PERCENTAGE
Unclassified	16	7.10
Benign hypertensive	15	6.70
Malignant hypertensive	9	4.00
Chronic vascular nephritis	1	0.45
Acute glomerulonephritis	1	0.45
Chronic glomerulonephritis	12	5.40
Mild pre-eclampsia	96	42.90
Severe pre-eclampsia	58	25.90
Eclampsia	16	7.10
Total	224	100.00

It is a simple and common-sense classification and omits conjectural and ambiguous conditions associated with pregnancy, as well as disturbances common to early pregnancy. Because of the lack of specific data to definitely classify them, 16 of our patients fell into the unclassified group. While some patients with marked tachycardia, dyspnea, hyperpyrexia, and a failure to respond to treatment are included, none was classified as eclamptic unless actual convulsions were present. Hypertensive toxemia and the various renal types were classified as such on the basis of involvement antedating the pregnancy or being present in early pregnancy, as well as on information gained in the late puerperium. One hundred seventy patients (75.9 per cent) in our series represent what we term *true* pregnancy toxemia, where the manifestations of toxemia were apparent only during the last three and one-half months of pregnancy. No cases are included where interruption of pregnancy or delivery occurred prior to six months of gestation.

The bony pelvis, as a factor governing the management of our cases, presented no problem. Table II reveals the relationship between the type of pelvis and the method of delivery.

Treatment

The object of our treatment is an attempt to return involved tissues and organs to, and to maintain them in, as nearly a physiologic capacity as possible. While we make no claim for treating any assumed cause of toxemia of pregnancy, our management of these patients is designed to treat and further prevent manifestations already demonstrated by the toxic patient. It is imperative that treatment be instituted early in order to prevent progression of seemingly insignificant findings, as well as to forestall latent sequelae. All too frequently, insouciance and procrastination in the management of novitiates of a toxemic career spell latent hypertension and nephritis, as pointed out by several investigators.[2-4]

Many normal parturients elicit one or more signs and symptoms represented in the complex which makes up the toxemias of pregnancy. While

many of these may be of a temporary nature, a review of the records of pregnancy toxemia patients reveals a sustained and progressive concatenation of such signs and symptoms. Likewise, the majority of severely pre-eclamptic and eclamptic patients are found, at some time during that pregnancy, to have been mildly pre-eclamptic. Too often the time interval between the initial appearance of very early signs and symptoms, without treatment, and the appearance of severe toxemia is so long that conservative treatment is of little value. It is for this reason, that attempt at control of even early symptoms and signs is advocated.

The general plan of our management of the toxemia patient is based upon the utilization of the neutral diet, ammonium chloride, abundant fluids, bed rest, sedation, and hospitalization.

Neutral Diet.—The neutral diet consists of foods which yield an equal amount of acid ash and alkaline ash, to which are added certain foods which yield an ash with no chemical reaction. These foods are prepared and served without the addition of salt and are especially selected because of their low sodium content. Bread is made without salt and sweet butter is used. The term neutral diet implies that the diet is salt free and sodium poor. It would therefore hold that foods preserved in salt such as ham, bacon, corned beef, smoked or salt water fish, pickles, and olives must be prohibited. Salt and soda form a common dentifrice and gargle and sodium bicarbonate and similar proprietary products are used for the relief of heart burn, common not only to the toxemia patient, but also frequently symptomatic in the normally pregnant individual. The diet is further characterized by a resultant ash which is neutral or slightly on the acid side.[5] Following is a list of foods used in the diet of the pregnant patient with toxemia, indicating the type of ash yielded by each.

FOODS WHICH YIELD

An Acid Ash:	*A Neutral Ash (or none):*	*A Basic Ash:*
Meat	Butter	Milk
Fish	Cooking fats	Cheese
Eggs	Salad oils	Vegetables
Cereals and their products	Sugar	Fruits (with the exceptions under "acid")
Breakfast cereals	Tapioca	Beans (lima kidney)
Bread	Gelatine	Almonds
Rice	Vinegar	Chestnuts
Macaroni	Cornstarch	
Spaghetti	Tea	
Hominy	Coffee	
Corn		
Lentels		
Peanuts		
Walnuts		
Prunes, Plums, Cranberries { containing benzoic acid which is conjugated with glycine and excreted as hippuric acid.		

TABLE II. TYPE OF PELVIS

	TYPE OF DELIVERY							
	NUMBER	CESAREAN SECTION	HYSTEROTOMY	FORCEPS	NORMAL SPONTANEOUS DELIVERY	VERSION AND EXTRACTION	DÜHRSSEN'S AND MIDFORCEPS	DESTRUCTIVE
Not known but parous	8		1	1	6			
Not known but nulliparous	7	1			6			
Normal	188	9	2	4	164	5	1	3
Android	13			1	12			
Platypelloid	8				8			
Severe contraction	0							
Total	224	10	3	6	196	5	1	3
Percentage	100	4.46	1.34	2.68	87.5	2.23	0.44	1.34

Since we are particularly desirous that weight gain be held to a maximum of 20 pounds for the total duration of pregnancy, the average neutral diet contains approximately 2,100 calories daily. The essentials of good nutrition are not sacrificed, and the protein content maintained from 85 to 100 Gm. daily. We are not convinced that high protein intake is instrumental in producing kidney damage where no previous damage existed. Neither are we convinced that a high protein diet does anything to enhance the progress of already existing renal disease in pregnant patients.

Following is a list of foods designed to meet the daily nutritional requirements of the toxemia of pregnancy patient, supplying 2,100 calories and 85 Gm. of protein and, at the same time, furnishing a neutral ash:

Meat or fish—1 large serving.
Eggs—3 (or 1 egg and 1 serving of meat or fish).
Bread—4 slices.
Cereal—1 serving (any cooked cereal). Puffed wheat or rice, Quaker shredded wheat.
Rice, macaroni or spaghetti—1 serving.
Milk—4 glasses.
Fruit—2 servings. } See
Vegetables. } List
Butter—6 pats.

If additional calories are needed, they can be supplied from salad oil, more bread, sugar, candy or a dessert using cereal (rice, cornstarch pudding, cake, cookies). The sodium chloride content of milk is low enough so that no significant water retention results if no more than one quart is taken daily.

Expressed in terms of meals to be provided to the patient, the above foods may be divided as follows:

Breakfast
Fruit (citrous)
Cereal
1 Egg
2 slices of toast
2 pats of butter
Coffee or tea

Lunch or Supper
Eggs—2 or meat or fish
Vegetable
Bread—1 slice
2 pats of butter
Milk—1 glass

Dinner
Meat or fish—1 serving
Vegetable—1 serving
Bread—1 slice
Butter—2 pats
Fruit—1 serving
Milk—1 glass
2 glasses of milk to be taken between meals.

An excessive weight gain in pregnancy toxemia patients, due to overeating, is more often the rule rather than the exception. In these overweight patients a neutral diet containing 1,400 to 1,500 calories may be secured by substituting skimmed for whole milk, using three teaspoons of butter, and by using fresh fruits or those canned without sugar.

Only the following fruits and vegetables are used:

3 Per Cent Vegetables
- Asparagus
- Cabbage
- Cauliflower
- Lettuce
- Mushrooms
- Radishes
- Tomatoes
- Tomato juice
- Celery
- Cucumber

12 Per Cent Fruit
- Apricots
- Cherries
- Oranges
- Orange juice
- Pineapple
- Raspberry juice

6 Per Cent Fruits
- Cantaloupe
- Watermelon

6 Per Cent Vegetables
- Pumpkin
- Squash
- String beans
- Turnips

15 Per Cent Fruit
- Apples
- Grapes
- Pears

15 Per Cent Vegetables
- Parsnips
- Peas

9 Per Cent Fruits
- Grapefruit
- Grapefruit juice

9 Per Cent Vegetables
- Beets
- Carrots
- Onions
- Rutabagas

Fluids.—While therapeutic recommendations of the amount of water necessary to treat the pregnancy toxemia patient have varied from one extreme to the other, there can be no debate that sufficient water is required to carry off such products of metabolism as the kidneys ordinarily excrete. Some ambiguity in the meaning of water balance seems to exist. We do not feel, as does Arnold,[6] that a patient is in water balance when ingested fluid equals the amount of water excreted as urine. As has been shown by Newburgh and his associates, normal water balance takes into account water excreted through the kidneys, skin, expired air, and stool. With established figures available on what water balance is in the normal nonpregnant[7-11] and in the normally pregnant[12] individual for a 24-hour period, our treatment is, in part, based on replacing fluids in such amounts as to insure the requirements for normal water metabolism. We have developed a definite "fluid consciousness" in the treatment of the toxemias of pregnancy. Fluids are forced to a level sufficiently high to produce urinary excretion approximately equal to the output of a normal individual. When the fluid intake reaches such a level, the requirements for water of expired air, perspiration, and water of stool are also satisfactorily supplied. Since the majority of our severely toxic patients show both clinical and laboratory evidence of dehydration, the first attempts in our management of these patients are designed to correct this dehydration and to approximate normal renal function as nearly as possible.

Fluids are supplied by mouth, parenterally, or by both routes, if necessary, in order to insure a minimum daily urinary output of 2,000 cubic centimeters. Frequently a daily minimum fluid intake of 4,000 cubic centimeters is necessary to effect the result of normal water balance. We wish to emphasize that inundation is not only impractical but unnecessary and fatuous. Since normal renal function signifies the excretion of waste products and solids in water, we feel that excretion of these products in large amounts of urine tends to

preserve the normal functioning capacity of the kidney instead of producing overtaxation of the physiologic renal unit. When intravenous fluids are administered, 5 per cent glucose in distilled water is given in order to avoid the attendant increased water retention accompanying the administration of glucose in saline or Ringer's solution. Likewise sodium bicarbonate or similar preparations are not given. Hypertonic solutions of glucose are not used since they must be converted to isotonic solutions by the liver in effecting normal water metabolism.

It is generally thought that forcing fluids in the toxemia patient will increase edema. This is true only when sodium bicarbonate or uncontrolled sodium chloride ingestion is permitted. In an experience with a few patients in this series, it was found that with drinking 8,000 to 9,000 c.c. of water daily, plus the other measures of therapy outlined here, there was no increase in edema, blood pressure, albuminuria, or weight gain. On the other hand, a small group of controlled patients were given large amounts of water with large amounts of salt and soda; this was followed by a sharp increase in weight gain, demonstrable edema and a significant rise in blood pressure. These patients were not continued on the high sodium intake to determine whether increased albuminuria would occur. All signs and symptoms disappeared after ammonium chloride, neutral diet, and forced fluids were resumed.

Ammonium Chloride.—Ammonium chloride is administered to release the sodium ion from the tissues and to release the intercellular fluid retained by the sodium. It is given in 0.5 Gm. gelatin capsules in order to insure complete absorption. Ammonium chloride in phenyl salicylate coated tablets has, in our experience, usually resulted in producing little or none of the desired effect, and, furthermore, the tablets have frequently been recovered unchanged in the stool. The capsules are given *with* the meals in order to reduce nausea and vomiting. The average dose is 3.0 Gm. (45 grains) three times daily and is continued for four days. To patients in coma or with convulsions, ammonium chloride may be administered through a stomach tube after convulsions have been controlled. The ammonium chloride is given in a 20 Gm. (300 grains) dose mixed with 250 c.c. of 40 per cent cream in order to limit gastric irritation. Also in this type of patient, ammonium chloride may be given intravenously (0.9 per cent solution in 1,000 c.c. 5 per cent glucose) with satisfactory response. The ammonium chloride breaks down in the gastro-intestinal tract and is absorbed as ammonium and chloride ion. After reaching the liver, the ammonium ion combines with CO_2 and H_2O to form ammonium carbonate which is converted to urea. The urea is excreted in the urine as such. The chloride ion combines with the sodium of the carbon-dioxide combining power of the blood in the extracellular spaces and is excreted through the kidneys as NaCl in water. The acid-base diagram, originally proposed by Gamble,[13] reveals an increased chloride concentration and a decrease in base bicarbonate. Since the kidney tends to reconvert urea to ammonium ion after prolonged ammonium chloride administration, ammonium chloride is therefore excreted as such. For this reason, ammonium chloride administration is not continued for periods longer than four days at a time. Its ingestion is then resumed after a rest period of three days. During these periods of administration a moderate inorganic acidosis is induced, but rarely does the CO_2 combining power fall below 45 volumes per cent if interrupted therapy is practiced.

Because the tissues of most severe toxemia patients are filled with water, due to the extracellular presence of enough sodium to retain water, the blood vascular system is usually dehydrated. Thus little of the retained fluid content of the body is made available to the circulating blood and to the kidneys. Since dehydration and oliguria are usually constant features of the severely toxic patient, an effort is made to combat this dehydration and to make water

available to the kidneys. With this increased fluid intake and a lowered sodium intake, more water is made available for its diuretic effect and for normal water metabolism. Ammonium chloride, in releasing extracellular water, further renders stored water available. In this manner, the extracellular spaces are dehydrated to normal and the blood vascular system hydrated, thus delivering additional water for urinary excretion of solids and waste products.

Sedation.—In the majority of cases little sedation is required, particularly in mild pre-eclampsia. Phenobarbital in doses of ½ to ¾ grain four times daily usually suffices. However in the severely toxic patient sodium phenobarbital given intramuscularly in 5 grain doses every five hours has proved a most satisfactory sedative. In toxemia with convulsions, we formerly favored the use of avertin in about one-half the basal anesthetic dosage. With a 50 mg. per kilogram dosage we encountered no patient whose convulsions were not promptly controlled. No manifestations of liver damage from avertin were noted. Because of the time required for preparation of the avertin and the consequent delay in controlling convulsions we no longer use avertin except in the occasional case. Instead, convulsions are brought under control by intravenous use of pentothal sodium 0.162 mg. This is repeated if necessary. After control of the convulsions, patients are satisfactorily and deeply sedated with intramuscular sodium phenobarbital (usually thirty-six to forty-eight hours) while medical measures of treatment of the toxemia are instituted and continued. When these patients reveal evidence of response to medical management, sedation is gradually diminished until consciousness is attained. Since the control of convulsions is not synonymous with the control of eclampsia, the patient is continued on treatment as a pre-eclamptic with the neutral diet, abundant fluids, ammonium chloride and a sedative dosage of barbiturates by mouth. Magnesi um sulfate was seldom used. The experimental utilization of veratrum viride in eight of our patients did not encourage its continued use.

Hospitalization.—In the presence of early signs and symptoms of a mild toxemia, patients are instructed on a neutral type of diet and given instruction on care at home. They are seen every third day in the clinic for checkup, but since the majority of these patients fail to improve at home, we feel that all early toxemia patients should have a short period of inculcation in home care during a preliminary period of hospitalization. All other types of toxemias are immediately hospitalized for complete care.

Special Measures.—Phlebotomy was performed in three of our cases, all of whom were severely toxic. In each instance there was evidence of left ventricular failure with pulmonary edema. Five hundred to seven hundred cubic centimeters of very concentrated blood the consistency of catsup were removed with resultant dramatic improvement. At the same time, intravenous 5 per cent glucose was slowly administered. None of the patients thus treated died. Oxygen therapy was used freely in the majority of our eclamptic or severely pre-eclamptic patients or where there was any evidence of cyanosis or dyspnea. Digitalis in one-half the digitalization dose was used in those with heart failure. None of the patients presented valvular heart disease.

The ocular fundus was investigated in 125 of our patients and the results recorded in Table III. Those patients showing ophthalmoscopic evidence of involvement and those showing no evidence of abnormal findings were about equally distributed.

Malignant hypertensive disease revealed significant retinal damage in 100 per cent of those examined. Unless vascular sclerosis was also present, patients were not classified in this group of toxemias.

Significant funduscopic findings were noted in over 50 per cent of the patients examined in almost every type of toxemia. Two patients were com-

TABLE III. FUNDUSCOPIC FINDINGS

	NUMBER CASES	PER CENT	UNCLASSIFIED	BENIGN H.B.P.	MALIGNANT H.B.P.	CHRONIC VASCULAR NEPHRITIS	ACUTE GLOMERULONEPHRITIS	CHRONIC GLOMERULONEPHRITIS	MILD PREECLAMPSIA	SEVERE PREECLAMPSIA	ECLAMPSIA
Normal	60	48	1	4	--	1	1	6	26	16	5
Generalized vascular disease, with or without spasm	38	30	--	3	--	--	--	4	13	14	4
Hypertensive neuroretinitis	19	15	--	--	4	--	--	--	3	8	4
Hypertensive neuroretinitis with hemorrhages, exudates, or both	8	7	--	--	3	--	--	2	--	2	1
Total	125	100	1	7	7	1	1	12	42	40	14

pletely amaurotic due to massive postretinal edema producing retinal detachment; under therapy the edema completely cleared and vision subsequently returned to normal. In evaluating the status of the ocular fundi as an indication for determining interruption of pregnancy or the efficacy of medical therapy, we have noted that the eye ground status does not tend to clear with the same rapidity as do the other manifestations of toxemia. For this reason, the persistence of retinal changes, in the presence of other clinical improvement, has led us to rely upon general clinical response rather than upon the ophthalmologist in determining the advisability of termination of pregnancy.

Response to Treatment

The majority of the patients responded favorably to our method of medical management as illustrated in Table IV.

TABLE IV. RESPONSE TO TREATMENT

TYPE OF TOXEMIA		NUMBER	NO TREATMENT	IMPROVED	NO CHANGE	PROGRESSIVE	MATERNAL MORTALITY
Unclassified		16	1	9	6	--	0
Benign hypertensive		15	--	12	3	--	0
Malignant hypertensive		9	2	1	3	3	3
Chronic vascular nephritis		1	--	1	--	--	0
Acute glomerulonephritis		1	--	1	--	--	0
Chronic glomerulonephritis		12	2	7	2	1	0
Mild pre-eclampsia		96	3	80	10	3	0
Severe pre-eclampsia		58	1	44	11	2	2
Eclampsia		16		14	2	--	1
Total	Number	224	9	169	37	9	6
	Per cent	100	4.01	75.4	16.5	4.01	2.67

While one malignant hypertensive exhibited evidence of improvement, the remainder of those treated showed no change in status or revealed definite progression of signs and symptoms. No improvement was anticipated in this group and since none resulted, we feel that these patients have nothing to gain by permitting the pregnancy to advance to the last trimester. Among those patients presenting no change or progressive signs of toxemia, the majority were in an extreme state of toxemia.

More than 80 per cent of the patients with so-called "true" toxemia of pregnancy (mild and severe pre-eclampsia and eclampsia) responded to our medical management. Especially well did the eclampsia group respond to medical treatment, and only one of these died.

Favorable response to treatment occurs within forty-eight hours after institution of treatment and patients usually continue to maintain a favorable course. Patients thus responding are kept on a conservative regimen until labor intervenes or, after sustained improvement at term, until labor is induced. If, after five to seven days of conservative treatment, there is no satisfactory response to treatment, we feel that termination of pregnancy by the most conservative means for that patient is indicated. We do not feel that indiscriminate termination of pregnancy is indicated just because a patient with an untreated toxemia has reached an arbitrary number of weeks of pregnancy.

Simrall,[14] in a follow-up study of 100 patients treated by this method, found no evidence of significant vascular or renal morbidity in patients known to be normal prior to their toxemic pregnancies.

Induction of Labor

The treatment of pregnancy toxemia embodies two general types of management: (1) medical, and (2) termination of pregnancy. In general the former treats the disease process complicating the pregnancy, while the latter treats the pregnancy. Many of the methods of interrupting a toxemic pregnancy have stressed the surgical rather than the obstetric approach. Such surgical intervention has accounted for many of the deaths ascribed to the toxemia. Termination of pregnancy, in our clinic, is now considered an *adjunct* to already established medical treatment only when such established treatment has failed to control the toxemia. When induction of labor is indicated, medical induction and/or rupture of the membranes are preferred and normal spontaneous delivery (including low forceps) the favored method of delivering these patients.

TABLE V. INDUCTION OF LABOR

	NUMBER	SPONTANEOUS	MEDICAL	RUPTURE OF MEMBRANES	INTRAOVULAR BAG	CESAREAN SECTION	HYSTEROTOMY
Unclassified	16	11	4	1			
Benign hypertensive	15	12	3				
Malignant hypertensive	9	5		2			2
Chronic vascular nephritis	1			1			
Acute glomerulo	1						1
Chronic glomerulo	12	8	3		1		
Mild pre-eclampsia	96	64	21	5	2	4	
Severe pre-eclampsia	58	36	12	3	3	4	
Eclampsia	16	6	1	4	3	2	
Total	224	142	44	16	9	10	3

There are those who advocate immediate termination of pregnancy where the following conditions prevail: (1) in the presence of convulsions; (2) if convulsions are believed to be inevitable; (3) if the medical regime appears to be endangering the patient's renal or ocular status; and (4) where no improvement occurred under medical treatment. For the most part, we favor interruption in 100 per cent of those showing no improvement under medical management. We believe that the first two situations are conditions requiring medical management until such time as these conditions are controlled or do not improve. As previously stated, funduscopic response to treatment does not keep pace with clinical response.

Cesarean Section

Cesarean section, as a satisfactory method of delivering the toxemia of pregnancy patient, presents subject material for endless debate. The proponents of cesarean section argue in terms of lowered maternal mortality. While there was no maternal mortality among our sectioned toxic patients, we are not prepared to advocate its use in the management of toxemia of pregnancy. On the basis of our and others' data, we feel that extra-toxemic factors should determine the indications for cesarean section. The cesarean operation was performed in 10 patients, an incidence of 4.5 per cent, and factors pertinent to these cases are set forth in Table VI.

Pelvic obstruction presented no indication for section except in one eclamptic primipara with such massive edema of the vulva as to preclude delivery by any other method. Previous cesarean section presented an indication for repeat section in three instances, one of which presented another real indication, total placenta previa. Abruptio placentae, diabetes and obstructive edema furnished the indications for celiotomy in one each. Since

TABLE VI. CESAREAN SECTIONS

YEAR	PARA	TYPE OF PELVIS	INDICATION FOR SECTION	TYPE OF TOXEMIA	DURATION OF PREGNANCY	DURATION OF TREATMENT PRIOR TO SECTION	REMARKS
1936	2	Normal	Previous section	Mild pre-eclampsia	Term	2 days	
1937	0	Normal	Eclampsia	Eclampsia	Term	Sectioned on admittance date	
1937	0	Normal	Severe pre-eclampsia	Severe pre-eclampsia	Term	1 day	
1939	5	Normal	Total placenta previa	Severe pre-eclampsia	Term	18 days—then developed signs of Pl. Pr.	Previous section
1939	0	Normal	Pre-eclampsia—failed to respond to treatment	Severe pre-eclampsia	Term	14 days (failure)	Primipara breech
1939	1	Normal	Diabetes and mild pre-eclampsia	Mild pre-eclampsia	8½ mo.	6 days	Section done to prevent stillbirth
1941	0	Normal	Mild pre-eclampsia	Mild pre-eclampsia	Term	Sectioned on admittance date	
1941	0	Not examined	Marked vulvar edema and eclampsia	Eclampsia	8½ mo.	2 days	Admitted in eclampsia
1941	3	Normal	Previous section	Mild pre-eclampsia	Term	1 day	
1943	1	Normal	Severe abruptio placentae	Severe pre-eclampsia	8½ mo.	Sectioned on admittance date	Dead fetus; hysterectomy performed

sectioning the diabetic patient with a mild pre-eclampsia at eight and one-half months of gestation, we have modified our former idea of delivering these patients by section.

Toxemia of pregnancy itself was considered an indication for cesarean section in four patients. Even though this method of delivery was used in these patients, we, again, do not feel prepared to recommend cesarean section for the treatment of toxemia. Although these patients were primiparas, we consider, on hind sight, that three of these four patients might well have been allowed to deliver normally after medical induction of labor. Failure to respond to treatment and a breech presentation in a primipara may constitute valid indications. Among these four patients sectioned because of their toxemia, it is probable that they could have been given a longer trial on medical management before delivery. These patients were sectioned during the first thirty-six hours of hospitalization without an adequate trial of medical management. We no longer subscribe to sectioning the eclamptic patient until a sufficiently adequate trial of medical therapy has determined the value or futility of such treatment. On the basis of our review, we feel that no hard and fast rules can be proposed regarding section except that we do not feel that uncontrolled eclamptics should be sectioned.

Eclampsia

Toxemia with convulsions occurred in 16 of our patients, an incidence of 7.1 per cent. No patient, even though in coma, was classified as eclamptic unless actual convulsions were or had been present. That eclampsia is an affliction of primiparas (81.3 per cent) is noted in Table VII. Only a small group of these eclamptic patients (18.7 per cent) received what might be interpreted as a beginning of prenatal care, varying from three to six months prior to delivery. The remainder received little or no care. Incomplete data on weight gain during pregnancy precludes any statement regarding any relationship to the development of eclampsia.

TABLE VII. ECLAMPSIA

NO.	CASE NO.	PARA	TIME INTERVAL BETWEEN FIRST ANTEPARTUM VISIT AND DELIVERY	DURATION OF TOXEMIA TREATMENT BETWEEN ECLAMPSIA AND DELIVERY	WEIGHT GAINED DURING PREGNANCY	DURATION OF PREGNANCY	INDUCTION OF LABOR	TYPE OF DELIVERY
1	353293	0	6 months	15 minutes	25 pounds in 6 mo.	9 mo.	Spontaneous	Low forceps
2	361549	0	1 month	5 minutes	Not known	9 mo.	Spontaneous	Normal
3	367931	12	None	2 hours 15 minutes	Not known	8½ mo.	Spontaneous	High forceps
4	372917	0	None	Delivered elsewhere	--	9 mo.	Spontaneous	Normal
5	380416	0	5 months	2 days	47 pounds in 5 mo.	8½ mo.	Bag	Destructive
6	392652	0	3 months	None	14 pounds in 3 mo.	9 mo.	--	Section
7	393394	0	None	2 days	Not known	8 mo.	Ruptured memb.	Low forceps
8	394637	0	None	3 hours	23 pounds	7½ mo.	Spontaneous	Normal
9	395757	0	None	11 hours 15 minutes	25 pounds in 3 mo.	8½ mo.	Medical	Normal
10	407383	0	6 weeks	None	10 pounds in 6 wk.	8½ mo.	Medical	Normal
11	412703	3	None	Delivered elsewhere	--	9 mo.	Spontaneous	Normal
12	438816	0	None	12 hours	Not known	9 mo.	Bag	Midforceps
13	444374	0	None	12 hours 15 minutes	Not known	6 mo.	Bag	Normal
14*	451428	8	None	15 hours 10 minutes	Not known	7½ mo.	Spontaneous	Normal
15	456120	0	None	33 hours 25 minutes	Not known	7 mo.	Spontaneous	Normal
16	484786	0	None	48 hours	Not known	8½ mo.	--	Section

*Maternal Death.
81.3% Primiparas.

Nine patients developed toxemia convulsions at or earlier than eight and one-half months of gestation, while only two artificial inductions were performed in patients whose pregnancy had advanced to less than eight and one-half months. Cesarean section was performed in two patients, one for soft tissue obstruction, the other for eclampsia itself.

Eclamptic patients, in our clinic, are generally managed conservatively. We feel that these patients should be given a trial of medical therapy to determine the ability to respond. If no improvement in status occurs or if symptoms and signs are progressive, we favor termination of pregnancy in the most conservative manner for that patient. As previously noted, patients with convulsions or coma are not fed for three days in order to develop a mild starvation acidosis. Convulsions are controlled by intravenous pentothal sodium and deep sedation maintained by intramuscular sodium luminal (5 grains every five hours) for the next forty-eight hours. Immediately after control of convulsions, crystalline ammonium chloride is administered by stomach tube, and 5 per cent glucose in water given intravenously to maintain a total 24-hour minimum intake of 4,000 cubic centimeters. When blood pressure, edema, and albuminuria subside, sedation is gradually decreased until food and fluids can be taken by mouth. The patient is then placed on the regimen for pre-eclampsia and thus maintained until delivery occurs or until failure of improvement indicates termination of pregnancy. Frequently during the first three days of treatment, the patient may void as much as 7,000 to 8,000 c.c. of urine per 24-hour period, with great loss of edema. Not uncommonly such diuresis is accompanied by a drop in albuminuria from four plus, to a trace, or none.

Mortality

Mortality figures are usually proportionate to the length of antepartum observation time, where keeness of the physician and cooperation of the patient simultaneously operate. Six of our patients died with, but not necessarily from, toxemia as noted in Table VIII.

TABLE VIII. MATERNAL MORTALITY

ADMITTED	DIED	DURATION OF ANTEPARTUM TREATMENT IN CLINIC	DURATION OF HOSPITAL TREATMENT	TOTAL TIME DURATION OF HOSPITALIZATION	TYPE OF DELIVERY	DURATION OF PREGNANCY	CAUSE OF DEATH	TYPE OF TOXEMIA
5:00 P.M. 3/28/35	7:45 P.M. 4/16/35	None	2 hours 45 minutes (antepartum) 19 days (postpartum)	19 days plus 2 hours 45 minutes	Low forceps	8 months	Pulmonary tuberculosis	Severe preeclampsia
2:15 P.M. 5/ 4/35	4:30 P.M. 5/ 4/35	None	None	2 hours 15 minutes	Undelivered	7½ months	Cerebral hemorrhage	Malignant hypertensive
11:00 A.M. 11/12/37	3:40 P.M. 11/14/37	None	24 hours (antepartum)	52 hours 40 minutes	Vaginal hysterotomy	6 months	Cerebral hemorrhage	Malignant hypertensive
10:15 A.M. 7/ 6/38	2:00 P.M. 7/ 6/38	None	None	3 hours 45 minutes	Low forceps	8 months	Atelectasis	Severe preeclampsia
11:30 A.M. 10/15/39	6:00 P.M. 10/16/39	None	21 hours (antepartum) 9 hours 30 minutes (postpartum)	30 hours 30 minutes	Normal	7½ months	Pulmonary edema	Eclampsia
5:45 P.M. 9/20/40	6:00 P.M. 9/23/40	2 months (totally unco-op)	6 hours (antepartum) 48 hours (postpartum)	54 hours	Normal	7½ months	Coma	Malignant hypertensive

The over-all maternal mortality rate was 2.67 per cent, while the malignant hypertensive group accounted for 50 per cent of the total mortality. The mortality rate in eclampsia was 6.25 per cent, while the rate due to preeclampsia was 1.3 per cent. We feel that most of the deaths were preventable, since the problem of maternal mortality control seems to be confined to a period considerably earlier than the time of appearance of the death-dealing factor. While the malignant hypertensive group presented evidence of disease early in pregnancy, which had already spelt their doom, we are able to state that pregnancy precipitated the gravity of this existing disease and was, in a large measure, the major factor in shortening life. Since the paramount object of good prenatal care is to reduce maternal mortality to zero, so must therapy consider lengthening life by rendering the change found in toxemia as ephemeral as possible. Such prenatal care must necessarily include a stentorian stand on interruption of pregnancy at the earliest sign of continued damage in spite of instituted remedial measures. In such patients where artificial termination is justified in the hypertensive and nephritic groups, permanent sterilization at the same time is also equally justified if we are to preserve an enviable record in diminishing this important cause of maternal death.

The gross fetal mortality was 14.2 per cent; the cause of death in the majority of instances was prematurity, while monstrosities accounted for four deaths.

Summary

1. Patients with toxemias of late pregnancy are generally managed conservatively.

2. Toxemias of pregnancy are treated according to a conservative regimen, consisting of hydration, neutral diet, ammonium chloride, bed rest, and mild sedation.

3. Conservative therapy of pregnancy toxemia embodies the modern principles of water balance.

4. When conservative methods fail to control pregnancy toxemia, termination of pregnancy is effected by the most conservative means suited to the particular individual.

5. The latent sequelae following pregnancy toxemia are minimized by such conservative therapy.

6. The indications for cesarean section in toxemia patients should be essentially the same as when no toxemia exists.

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THE DETERMINATION OF REDUCING SUBSTANCES IN HUMAN CERVICAL MUCUS*

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IT IS now known that the cervical mucus of normally menstruating women is most abundant, most translucent and acellular, and possessed of lowest viscosity at midcycle, i.e., when ovulation is believed to occur.[1-7] The viscosity of cervical mucus is believed to be an important factor in governing the ease with which the spermatozoa can invade this medium, since they can penetrate the mucus for an appreciable distance only at the time of lowest viscosity.[1-4, 7, 8] Other properties of the mucus may, however, be operative in aiding or hindering the migration of spermatozoa through the cervical canal.

The widespread distribution of glycogen and its hydrolytic products in the female generative tract would appear to have functional significance. According to Hughes[9] and Novak,[10] glycogen serves as an important nutritive agent for the ovum before and after nidation. Similarly, the presence of glucose in the seminal fluid seems to be important for sperm nutrition. According to McCarthy[11] the concentration of glucose in the fresh ejaculate, which averages 300 milligrams per cent,[11-13] is reduced to 10 to 25 per cent of this level by incubation of the semen for twenty-four hours. This diminution suggests utilization of glucose by the spermatozoa. MacLeod[14, 15] found that the metabolism of human spermatozoa suspended in Ringer-glucose solution is largely glycolytic and that substrates containing such sugars as glucose, maltose, mannose, fructose, and glycogen are required for glycolysis and for the prolonged activity of the spermatozoa. He also suggested[15] that there may be a suitable substrate in the female generative tract to maintain the motility of the spermatozoa, since it would appear that individual spermatozoa carry with them no appreciable quantity of extracellular nutritive matter when they invade the cervical mucus. This suggestion led to the present study of the presence of glucose, related reducing substances, or their precursors in cervical mucus.

Methods

Subjects.—Young healthy women who had normal menstrual histories and normal pelvic structures served as subjects for this study.

Collection of Mucus.—An unlubricated speculum was inserted to expose the cervix. Mucus covering the area of the external os was aspirated with a glass cannula of known weight. Specimens obtained in this manner were considered as "draining" specimens. These were undoubtedly contaminated to varying degrees by the vaginal contents. The cervical canal was then aspirated as completely as possible with a second glass cannula of known weight, and the material thus procured was considered a "canal" specimen. The filled cannulae were weighed and the amount of mucus was determined by difference. Analyses were carried out separately on both types of specimens.

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The amount of mucus available for analysis at midcycle ranged from approximately 100 to 400 milligrams. At other times in the cycle, i.e., in the pre- and postovulatory phases, the amount of mucus obtained was greatly reduced, 15 to 50 milligrams being representative. Specimens weighing less than 10 milligrams did not lend themselves to analysis.

Water Content.—The water content of the mucus was determined by drying specimens to constant weight in an oven at 55° C.

Measurement of Reducing Substances.—The Shaffer-Hartman copper reagent as modified by Somogyi[16] was used throughout these studies. By using this reagent it is possible to determine quantitatively very small amounts of reducing substance since the cuprous oxide formed is not easily reoxidized. Furthermore, this reagent is not as readily reduced by substances other than glucose as are some of the other reagents in common use.

The heating period with 2 c.c. of the copper reagent added to the samples was twenty minutes in a boiling water bath. After acidification with 3 c.c. of 1 N sulfuric acid, the usual iodometric titration was carried out with sodium thiosulfate. A standard glucose curve was determined, and all the results were expressed as milligrams per cent glucose.

1. *Free reducing substance:* The copper reagent was added to a weighed quantity of mucus and the amount of reducing substance determined as outlined above.

2. *Total reducing substance:* A weighed amount of mucus was hydrolyzed in 2 c.c. of 1 N sulfuric acid for three hours in a boiling water bath. The solution was then neutralized with 2 N sodium hydroxide, using phenolphthalein as the indicator. The copper reagent was then added and the amount of reducing substance determined.

3. *Per cent fermentable reducing substance:* Hydrolysis of the mucus specimen was carried out as in the determination of total reducing substance. After neutralization with the sodium hydroxide the volume was brought to 10 c.c. A 4 c.c. aliquot was used for the determination of total reducing substance. A 5 c.c. aliquot was fermented for fifteen minutes at approximately 37° C. with yeast.* After centrifuging, 4 c.c. of the supernatant were used to determine the amount of reducing substance remaining. The difference between the reducing substance values before and after fermentation gave the amount of fermentable material, presumably glucose.

4. *Free reducing substance in precipitate:* A known amount of cervical mucus was digested with 1 c.c. of 30 per cent potassium hydroxide, 3 c.c. of 95 per cent alcohol were added, and the tubes were then allowed to stand overnight in the refrigerator. This is a standard procedure for the precipitation of glycogen. After centrifuging, the supernatant was decanted for separate analysis.

The precipitate was dissolved in 1 c.c. of distilled water, the copper reagent was added, and the amount of reducing substance determined.

5. *Free reducing substance in supernatant:* The alcohol in the supernatant obtained by the precipitation method described above was evaporated off in a boiling water bath. The solution was then neutralized with sulfuric acid, the copper reagent was added, and the amount of reducing substance determined.

6. *Total reducing substance in precipitate:* The total amount of reducing substance in the precipitate obtained as described above was determined in the same manner as for total reducing substance in mucus. In some cases the specimen was divided into aliquots after hydrolysis and neutralization. One aliquot was used for the determination of total reducing substance, and the other was fermented with yeast.

*Twenty grams of baker's yeast were washed three times with 50 c.c. portions of distilled water and were than suspended in 50 c.c. of water. Three c.c. of this suspension were centrifuged and the cells were used for the fermentation study.[17]

Calculation of results: The cycles, exclusive of the menstrual period, were divided into three phases. The ovulatory phase encompassed those days in midcycle on which the amount of mucus was markedly increased. The preovulatory phase took in the period between the last day of menstruation and the ovulatory phase, and the postovulatory phase, the period from the end of the ovulatory phase to the onset of the next menstrual period. The daily results from all the cycles studied were averaged according to the phase of the cycle and grouped for comparison.

Wherever possible the data were subjected to a statistical analysis and the probabilities (P) as calculated by use of the Fisher "t" are given in the tables. When the value of P was less than 0.05, the differences were considered to be significant.

Results

In a preliminary publication[18] cyclic variations in the water content and in the concentration of reducing substances of cervical mucus were described. The water content (Table I) increases significantly in the ovulatory phase for

TABLE I. WATER CONTENT OF CERVICAL MUCUS

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	38	33	51	33	48	50
Number of subjects	3	3	3	3	3	3
Number of cycles	9	10	10	9	10	10
Range, per cent water	90.2-96.6	93.1-97.7	90.5-96.3	93.9-98.6	96.0-98.8	91.4-97.0
Average, per cent water*	93.6	95.2	93.0	95.9	97.9	94.8
Standard deviation	2.7	2.7	1.8	2.0	2.2	2.9
Averaged on basis of opalescence						
Marked	93.5 (31)†	94.4 (7)	93.0 (51)	95.5 (14)	----	94.4 (34)
Moderate	94.2 (7)	95.3 (20)	----	96.2 (16)	97.2 (5)	95.7 (15)
Negligible	----	96.0 (6)	----	96.6 (3)	98.0 (43)	95.8 (1)

*The probabilities (P) of significant differences in water content have been calculated by the use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, $P = 0.014$
Postovulatory compared to ovulatory, $P = 0.0001$
Preovulatory compared to postovulatory, $P = 0.23$

Canal: Preovulatory compared to ovulatory, $P = <0.0001$
Postovulatory compared to ovulatory, $P = <0.0001$
Preovulatory compared to postovulatory, $P = 0.5$

†Number of specimens indicated in parentheses.

both draining and canal samples, although the water content of the draining specimens is consistently lower than for the canal specimens. This difference between the two types of specimens proved to be statistically significant.

The concentration of reducing substances as determined by the various methods are shown in Tables II to VII. With the single exception of the per cent fermentable reducing substance in the draining specimens, which showed no cyclic variation, there is a significant decrease in the concentration of reducing substance in the ovulatory phase of the cycle. This decrease is real and not merely due to dilution, for the concentration is lower in the ovulatory phase even when the calculations are made on a dry weight basis (Table VIII).

There is very little, if any, free reducing substance in the precipitate obtained by the precipitation method (Table V). Many values actually were zero, and for many more the amount of thiosulfate needed in the titration was

TABLE II. FREE REDUCING SUBSTANCE IN CERVICAL MUCUS

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	16	12	34	22	28	32
Number of subjects	5	5	5	5	5	4
Number of cycles	8	6	7	8	6	6
Range, mg. per cent	50-300	30-100	60-280	40-340	0-80	50-340
Average, mg. per cent*	130	52	133	122	37	150
Standard deviation	75	18	63	71	22	65
Averaged on basis of opalescence						
Marked	131 (15)†	70 (2)	135 (33)	153 (12)	----	163 (24)
Moderate		50 (7)	60 (1)	91 (8)	70 (2)	114 (5)
Negligible	110 (1)	43 (3)	----	55 (2)	35 (26)	107 (3)

*The probabilities (P) of significant differences in free reducing substance have been calculated by use of the Fisher "t."

Draining: Prevulatory compared to ovulatory, P = 0.0008
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.9

Canal: Preovulatory compared to ovulatory, P = <0.0001
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.15

†Number of specimens indicated in parentheses.

TABLE III. TOTAL REDUCING SUBSTANCE IN CERVICAL MUCUS

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	19	27	56	35	65	56
Number of subjects	7	7	9	7	9	9
Number of cycles	8	10	15	11	14	16
Range, mg. per cent	250-1160	160-990	360-1490	300-1480	110-640	290-2200
Average, mg. per cent*	688	438	848	728	266	875
Standard deviation	226	192	253	270	114	308
Averaged on basis of opalescence						
Marked	720 (13)†	----	881 (51)	825 (11)	----	963 (42)
Moderate	620 (6)	598 (10)	537 (3)	802 (15)	560 (2)	596 (7)
Negligible	----	344 (17)	495 (2)	488 (9)	256 (63)	626 (7)

*The probabilities (P) of significant differences in total reducing substance have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, P = 0.001
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.022

Canal: Preovulatory compared to ovulatory, P = <0.0001
Postovulatory compared to ovulatory, P = <0.0001
Preovulatory compared to postovulatory, P = 0.016

†Number of specimens indicated in parentheses.

so small as to be of questionable significance. These precipitates were not washed, since the amount of material obtained was very small, and it may be that a small amount of the supernatant solution remained in the tube and contributed to the values obtained.

Although a positive iodine test suggesting the presence of glycogen is given by the precipitate from the precipitation method, the amount of fermentable material measured after hydrolysis is not sufficient to indicate that this precipitate is glycogen alone. The evidence indicates that this precipitate contains other reducing substances which are not fermentable.

TABLE IV. PER CENT FERMENTABLE REDUCING SUBSTANCE

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	10	9	27	17	39	21
Number of subjects	4	4	8	5	7	8
Number of cycles	4	5	10	6	9	11
Range, per cent fermentable	36.4-76.7	39.5-77.8	28.0-80.7	23.9-71.6	8.7-62.5	28.6-77.9
Average, per cent fermentable*	54.8	60.8	59.9	44.6	36.4	50.7
Standard deviation	12.5	11.5	12.7	13.8	13.4	12.3
Averaged on basis of opalescence						
Marked	57.1 (8)†	----	59.9 (26)	49.5 (8)	----	51.7 (20)
Moderate	45.8 (2)	65.6 (5)	----	39.2 (8)	----	28.6 (1)
Negligible		54.7 (4)	59.5 (1)	48.1 (1)	36.4 (39)	----

*The probabilities (P) of significant differences in per cent fermentable glucose have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, $P = 0.35$
Postovulatory compared to ovulatory, $P = 0.85$
Preovulatory compared to postovulatory, $P = 0.27$

Canal: Preovulatory compared to ovulatory, $P = 0.038$
Postovulatory compared to ovulatory, $P = <0.0001$
Preovulatory compared to postovulatory, $P = 0.15$

†Number of specimens indicated in parentheses.

TABLE V. FREE REDUCING SUBSTANCE IN PRECIPITATE

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	5	9	17	12	35	20
Number of subjects	3	5	4	5	5	4
Number of cycles	3	6	5	5	7	5
Range, mg. per cent	10-30	0-20	0-100	0-60	0-20	0-100
Average, mg. per cent	24	7	28	17	6	25
Standard deviation	8	6	30	22	7	32
Averaged on basis of opalescence						
Marked	24 (5)*	----	29 (16)	23 (6)	----	31 (15)
Moderate	----	10 (1)	10 (1)	6 (5)	----	0 (3)
Negligible	----	6 (8)	----	30 (1)	6 (35)	15 (2)

*Number of specimens indicated in parentheses.

It is interesting to note that the concentration of free reducing substance as measured in cervical mucus directly (Table II) and the concentration of free reducing substance in the supernatant (Table VI) are strikingly similar. This supernatant gives a positive biuret reaction while the corresponding precipitate does not. The mucus itself also gives a positive biuret test. Hewitt[19] has shown that tyrosine and tryptophane will reduce the Hagedorn-Jensen reagent used for determining glucose almost as well as glucose itself. The presence of tyrosine and tryptophane in cervical mucus has been previously shown,[18] and it may well be that these, and possibly other amino acids, are contributing to the reduction of the copper reagent. These may also contribute appreciably to the amount of total reducing substance in cervical

TABLE VI. FREE REDUCING SUBSTANCE IN SUPERNATANT

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	5	9	16	12	35	19
Number of subjects	3	5	4	5	5	4
Number of cycles	3	6	5	5	7	4
Range, mg. per cent	60-140	20-60	50-300	60-320	20-70	0-220
Average, mg. per cent*	96	40	154	124	38	123
Standard deviation	33	14	54	68	15	54
Averaged on basis of opalescence						
Marked	100 (4)†	----	161 (15)	157 (6)	----	145 (14)
Moderate	80 (1)	50 (1)	50 (1)	92 (5)	----	75 (2)
Negligible	----	39 (8)	----	90 (1)	38 (35)	80 (2)

*The probabilities (P) of significant differences in free reducing substance in the supernatant have been calculated by the use of the Fisher "t."

Draining: Not enough samples for statistical analysis.

Canal. Preovulatory compared to ovulatory, $P = 0.0001$
Postovulatory compared to ovulatory, $P = <0.0001$
Preovulatory compared to postovulatory, $P = 1.0$

†Number of specimens indicated in parentheses.

TABLE VII. TOTAL REDUCING SUBSTANCE IN PRECIPITATE

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Number of specimens	22	28	35	33	63	41
Number of subjects	3	4	5	4	6	6
Number of cycles	7	8	8	8	11	9
Range, mg. per cent	90-270	40-560	120-670	40-300	0-190	60-630
Average, mg. per cent*	310	173	285	145	60	192
Standard deviation	150	129	112	68	43	115
Averaged on basis of opalescence						
Marked	303 (18)†	305 (2)	298 (32)	181 (16)	----	229 (28)
Moderate	340 (4)	168 (24)	143 (3)	110 (15)	73 (6)	108 (11)
Negligible	----	100 (2)	----	130 (2)	58 (57)	135 (2)

*The probabilities (P) of significant differences in total reducing substance in the precipitate have been calculated by use of the Fisher "t."

Draining: Preovulatory compared to ovulatory, $P = 0.0013$
Postovulatory compared to ovulatory, $P = 0.0007$
Preovulatory compared to postovulatory, $P = 0.5$

Canal: Preovulatory compared to ovulatory, $P = <0.0001$
Postovulatory compared to ovulatory, $P = <0.0001$
Preovulatory compared to postovulatory, $P = 0.029$

†Number of specimens indicated in parentheses.

mucus since the amount of fermentable material after hydrolysis accounts for less than 50 per cent of the total amount of reducing substance measured (Table IV).

Theoretically, the sum of the total amount of reducing substance obtained by hydrolysis of both the precipitate and the supernatant from the precipitation method should equal the total amount of reducing substance obtained by direct hydrolysis of the mucus. However, on direct hydrolysis a much higher concentration was always obtained. The supernatant is strongly alkaline and it may be that this has a deleterious effect on whatever reducing substances are contained in it. Further investigation into this fraction is necessary before definite conclusions can be drawn.

TABLE VIII. PER CENT CONCENTRATION OF REDUCING SUBSTANCES IN CERVICAL MUCUS CALCULATED ON A DRY WEIGHT BASIS

	DRAINING SPECIMENS			CANAL SPECIMENS		
	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE	PRE-OVULATORY PHASE	OVULATORY PHASE	POST-OVULATORY PHASE
Free reducing substance in cervical mucus	2.03	1.08	1.90	2.98	1.76	2.88
Total reducing substance in cervical mucus	10.75	9.13	12.11	17.76	12.67	16.83
Free reducing substance in precipitate	0.38	0.15	0.40	0.41	0.29	0.48
Free reducing substance in supernatant	1.50	0.83	2.20	3.02	1.81	2.37
Total reducing substance in precipitate	4.84	3.60	4.07	3.54	2.86	3.69

One of the most striking changes occurring at midcycle is the altered appearance of the cervical mucus.[1-7] Prior to the ovulatory phase the mucus is very cellular, giving it an opalescent appearance. Coincident with the increase in amount and increase in water content is a marked decrease in cellularity. The mucus becomes translucent and only very small patches of cellular material are occasionally visible to the naked eye. It has not been possible to determine the opalescence of cervical mucus in an objective fashion because of the difficulty in obtaining a satisfactory dispersal of the mucus with its cells over a grille. Therefore the opalescence has been estimated subjectively as marked, moderate, or negligible. Even this approximation has been sufficient to indicate a possible relationship between the degree of opalescence and both the water content and the concentration of reducing substances. It can be seen in the various tables that in general the more marked the opalescence the less the water content and the greater the concentration of reducing substances. To determine whether the chemical constituents found in cervical mucus are contained within the cells themselves or are in the extracellular portion is a problem for future study. The draining specimens are undoubtedly contaminated by the vaginal contents and only rarely is a completely translucent draining specimen obtained in midcycle as compared to the invariably clear canal samples procured at this time. The draining specimens contain significantly less water in all three phases of the cycle and significantly more reducing substance in the ovulatory phase than do the canal specimens.

Discussion

At present we may only speculate as to the significance of these findings. As stated earlier, MacLeod has shown that spermatozoa require a utilizable carbohydrate such as glucose, fructose, maltose, mannose or glycogen as a substrate in order to maintain their motility.[14, 15] He has also shown that in a glucose-free medium at body temperature many spermatozoa lose their motility completely within as short a time as two hours, whereas if adequate glucose is present and the oxygen tension is low, maximal motility is retained at least twelve hours in vitro.[15] He has determined that the effective concentration of utilizable sugar lies between 20 and 200 milligrams per cent.[14]

It is unlikely that spermatozoa carry with them any appreciable quantity of glucose from the semen as they enter the cervical mucus, yet motile sperm

can be found in mucus aspirated from within the cervical canal as long as thirty-six to eighty hours after coitus.[20-22] Even though many spermatozoa probably penetrate beyond the cervical canal so quickly in the ovulatory phase of the cycle as to have no need of a substrate as far as the cervical canal is concerned, the fact that those remaining in the canal are still motile many hours later suggests that some utilizable substrate is available to them there.

The data from the present studies show that the concentration of fermentable reducing substance present in the cervical mucus in the canal in the ovulatory phase, even though it is significantly lower than in the pre- and postovulatory phases, is still 97 milligrams per cent. This is well within the range of concentration of 20 to 200 milligrams per cent as determined by MacLeod.[14]

Summary

In the ovulatory phase of the normal menstrual cycle when the quantity of cervical mucus is greatest, the water content is increased and the cell count, as estimated on the basis of opalescence, is decreased. Throughout the menstrual cycle the mucus is found to contain free reducing substance. On hydrolysis additional quantities of reducing substance are found, approximately 50 per cent of which are fermentable with yeast. When cervical mucus is alkalinized and alcohol is added, a precipitate is formed which yields appreciable quantities of reducing substance only after hydrolysis. The supernatant contains free reducing substances in amounts comparable to the free reducing substance in mucus itself. Since the presence of amino acids has been demonstrated in cervical mucus it is suggested that these contribute to the measurement of reducing substance in some of the fractions. These various reducing substances are present in lowest concentration in the ovulatory phase, even when calculated on a dry weight basis. The possible significance of these findings with reference to sperm metabolism is discussed.

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CONCEPTION FOLLOWING THE PREDICTION OF THE DAY OF OVULATION WITH THE RAT TEST*

A Study of Ten Patients

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IN A previous communication, one of us (E. J. F.), described a new method for predicting the probable day of ovulation in women,[1] and in a following paper, reported some observations on the accuracy of the procedure as indicated by immediate laparotomy upon the monkey.[2]

Utilizing this test in the study of relatively infertile couples, intercourse or artificial insemination practiced on the predicted day of ovulation has resulted in some 50 conceptions. The present report deals with 11 conceptions experienced by 10 patients who came under the observation of both authors. The observations made in the handling of these women illustrate the use of the method, and indicate some of the problems which have been encountered in its application.

Materials and Methods

The first step in the study of each couple was an analysis of the husband's semen. The second procedure was an investigation of the patency of the wife's Fallopian tubes. This was followed by a timing of the day of ovulation.

Investigation of Husband.—The semen was analyzed following five days of sexual abstinence. The husband was then classified as being (1) infertile, (2) low fertile, or (3) highly fertile. The criteria for this classification will be described in a later publication by one of us (E. J. F.). The sperm counts recorded in this report refer to the total number of moving cells in the whole ejaculate.[3]

Investigation of the Wife.—In the absence of previous pregnancies or laparotomies, the patency of the Fallopian tubes usually was determined by uterosalpingography.

The probable date of ovulation was detected by the use of the rat test.

Specimens of urine collected on 10 consecutive days during the middle third of the patient's menstrual month were tested.

The technique of the test is as follows: 2 c.c. of the urine which the patient passes on arising in the morning are injected subcutaneously into each of two immature, female white rats of the Wistar strain. Each animal is killed by illuminating gas at the end of two hours. The abdomen is opened; the 2 ovaries are drawn, one at a time, into the wound, and the color of each is compared with the graded shades of red of the Munsell color system.

In the presence of normal ovulation, the patient's urine induces hyperemia in the ovaries of the rat on four or five consecutive days. In the total absence of ovulation, there is no hyperemia of the rats' ovaries. If the ovulation process is abnormal, hyperemia occurs, but usually not on four consecutive days. Intercourse is interdicted during the urine testing period of each month.

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The first month is utilized as a control. No attempt at conception is advised during this month. This control month supplies information upon whether there is any ovulation activity that can be detected, whether detectable activity is normal or abnormal, and if normal, the day in the cycle when ovulation takes place. Our evidence indicates that the egg is ready for fertilization on the last day of the color reaction.

During the months following the control month, intercourse is advised, or artificial insemination is performed on the last day of each normal ovulation reaction. No attempt at conception is advised, however, if the reaction is not normal.

Intercourse is interdicted during every testing period, since the act affects adversely the color reaction. It is especially important that intercourse is not practiced on the days immediately prior to the day when the egg is ready for fertilization, otherwise there will not be the maximum number of sperm available for that day.

Results

Ten women became pregnant when coitus or artificial insemination was timed with the day of ovulation. All but one of these patients had had difficulty in conceiving, prior to the time of her successful impregnation.

CASE 1.—This patient had been married for seven years. For three and one-half years she had been unable to become pregnant. Her husband was found to have no sperm cells. The patient's Fallopian tubes were revealed to be patent by uterosalpingography.

The details of the ovulation timing appear in Table I. The menstrual cycles were quite regular, and the patient's ovulation reactions with one exception were normal. Intrauterine insemination with the cells of a donor was practiced twice. In the first instance the insemination failed. It is believed that this failure was due to the fact that the semen of the first donor contained only 12,000,000 moving sperm cells in the total ejaculate.

The second insemination was successful. The semen of this donor contained 228,000,000 moving sperm cells in the total ejaculate.

TABLE I. CASE 1

OVULATION TESTS	MENSTRUAL CYCLE		COMMENTS
	OVULATION ON CYCLE DAY	LENGTH IN DAYS	
1	12	26	Control month. Reaction normal
2	12	26	Donor infertile. Intrauterine insemination failed
3	Abnormal	27	No attempt to conceive
4	13	27	Control month. Reaction normal
5	13	--	Donor fertile. Intrauterine insemination 2 P.M. Ovulation cycle day 13—conception followed

CASE 2.—This patient had been married for ten years without becoming pregnant. Her husband was normally fertile with 238,000,000 moving cells in the total ejaculate. The fimbriated ends of both Fallopian tubes of the patient were discovered to be closed by uterosalpingography. Bilateral salpingostomy was performed.

The details of the ovulation timing appear in Table II. Three attempts at conception were made following salpingostomy. Two of these were unsuccessful. The first failure is explained on the ground that the ovulation reaction was abnormal. The second failure is explained on the fact that coitus occurred on days 8 and 9 of the menstrual cycle when ovulation took place on day 10. The

natural decrease in the sperm count, which normally occurs following closely repeated ejaculations, probably accounted for the failure in this instance.

TABLE II. CASE 2

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	11	27	Control month. Reaction normal
2	Abnormal	30	Coitus P.M. cycle day 9 and A.M. cycle day 10. Failure due to abnormal reaction
3	10	25	Coitus P.M. cycle days 8 and 9. Failure due to reduced sperm count from coitus prior to ovulation
4	Abnormal	28	No coitus
5	12	--	Coitus on cycle day 12. Conception followed

The successful coitus took place on the day of ovulation which was day 12 of the cycle. It was the last day of a 4-day color in the rat ovaries. A tubal gestation resulted which was terminated by salpingectomy.

CASE 3.—This patient had been married for five years with inability to become pregnant for two years. Her husband's semen contained 266,000,000 moving cells in the entire ejaculate. The wife's Fallopian tubes were proved to be patent by uterosalpingography.

The details of the ovulation timing appear in Table III.

TABLE III. CASE 3

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	Abnormal (13)	25	Seven-day color reaction. Ovulation probably on cycle day 13
2	Abnormal (11)	25	Six-day color reaction. Ovulation probably on cycle day 11
3	11	--	Coitus on cycle day 11, the fourth day of color reaction. Conception followed

Ovulation was timed through three consecutive months. The ovulation reactions of the first two months were abnormal. Conception occurred during the first normal month, when coitus was practiced on the fourth day of the rat color reaction, which was the eleventh day of the menstrual cycle.

CASE 4.—This patient had been married for eighteen months with inability to conceive for the last twelve months. Her husband was reported by a urologist to be, in all probability, sterile. The patency of the wife's tubes was not tested.

The details of the ovulation timing appear in Table IV.

Ovulation day was timed for a period of six months. The reaction was normal five times. Coitus was practiced during each of the six months of testing. It failed to result in conception five times. Three of the failures can be explained on the ground that coitus was performed before the day of ovulation. In the first of these three months, it was practiced on day 11 when ovulation took place on day 14. In the second month, it was performed on day 11 when ovulation occurred on day 13. The third of these three failures was due to the fact that coitus was practiced on day 8 when ovulation took place on day 11. Repeated coitus, previous to the day of ovulation, results in a lowered sperm count on the day of ovulation.

TABLE IV. CASE 4

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	14	26	Coitus on cycle day 11 and for 4 consecutive days. Failure due to wrong timing of coitus and low sperm count on day of ovulation
2	13	25	Coitus on cycle day 11, second day of color, and repeated next day. Failure due to wrong timing of coitus and low sperm count on day of ovulation
3	Abnormal	27	Coitus on days 12, 13, and 14. No conception predicted on account of abnormal reaction
4	11	26	Coitus on cycle day 8 and for 4 consecutive days. Failure predicted on account of failure in timing and low sperm count on day of ovulation
5	11	26	Coitus on cycle day 12, and on 2 following days during a negative reaction. Failure predicted on account of wrong timing. Ovulation had occurred
6	11	--	Coitus on cycle day 11, the fourth day of color reaction. Conception occurred

One failure to conceive was due to the presence of an abnormal ovulation reaction. The last failure was due to the fact that coitus was practiced for the first time on the day after the ovulation reaction had ended.

The successful coitus took place on the predicted day of ovulation, which was the fourth and last day of a normal color reaction. It was also day 11 of the menstrual cycle.

CASE 5.—This patient had been married for thirteen years and had had two planned pregnancies. Her husband was highly fertile, possessing a sperm count of 300,000,000 moving cells in the entire ejaculate. No test of tubal patency was made.

The ovulation timing is shown in Table V.

TABLE V. CASE 5

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	8	Average (25 days)	Conception followed 1 coitus on eighth day

Ovulation was tested only once. It took place on the eighth day of an average 25-day cycle. Coitus on this day was followed by conception.

CASE 6.—This patient had been married for two and one-half years, and had failed to conceive for two years. Her husband was declared to be practically sterile by a urologist, and was treated with gonadogen. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The record of ovulation timing appears in Table VI.

Coitus was practiced during two months of testing. The first attempt failed. This is explained on the ground that the ovulation reaction was abnormal, and also because coitus was practiced two days before the probable day of ovulation.

The successful coitus was performed twice on the last day of a normal 4-day rat color reaction, which was day 9 of an average 26-day cycle.

TABLE VI. CASE 6

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	Abnormal (11)	25	Control month. Abnormal reaction following uterosalpingography. Ovulation probably cycle day 11
2	11	26	Control month. Dilatation and curettage
3	Abnormal (11)	28	Coitus on cycle days 9 and 10. Failure anticipated due to wrong timing and to abnormal reaction
4	9	--	Coitus twice on cycle day 9. Conception followed

TABLE VII. CASE 7

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
		First Pregnancy	
1	13	--	Coitus day 12, P.M. and day 13, A.M. Conception followed
		Second Pregnancy	
1	Abnormal	29	Control month
2	16	28	Coitus on day 14
3	13	--	Coitus days 13 and 14. Conception followed

CASE 7.—This patient had been married for four years and had had one previous pregnancy. Her husband was highly fertile with 373,000,000 moving sperm cells in the total ejaculate. The patency of the wife's Fallopian tubes was not tested.

The details of the ovulation timing appear in Table VII.

This patient was timed for two pregnancies. In the case of the first conception, success was achieved when coitus was practiced at midnight the day before ovulation and early in the morning of the day of ovulation.

Preceding the second conception, three ovulation tests were made. The first ovulation reaction was abnormal. Attempts at conception were made during each of the following test months. The first attempt was a failure. This is explained on the ground that the coitus took place two days before ovulation. The second attempt was successful. Here, coitus was practiced on the day of ovulation and on the succeeding day.

CASE 8.—This patient had been married for five years with failure to conceive for eighteen months. The husband possessed 158,000,000 moving cells in the entire ejaculate. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The details of the ovulation timing appear in Table VIII.

TABLE VIII. CASE 8

OVULATION TESTS	MENSTRUAL CYCLE: OVULATION ON CYCLE DAY	MENSTRUAL CYCLE: LENGTH IN DAYS	COMMENTS
1	Abnormal	31	----------
2	12	27	Normal control
3	Abnormal	25	Coitus days 13, 14, 15. Prediction—no conception
4	Abnormal	28	Coitus days 12, 13, 14. Prediction—no conception
5	10	--	Coitus days 10, 11, 12. Conception followed

Ovulation was timed during five consecutive months. For three months, the ovulation reaction was abnormal, and one month was used as a control. Coitus was practiced, but conception failed during two of the months when the reaction was abnormal. The fifth month produced a normal 4-day rat color reaction, which resulted in ovulation on the tenth day of the cycle. Conception followed coitus practiced on that day. The selection of that day was based upon timing and observations which were carried out during the preceding months.

CASE 9.—This patient was married for 11 years. She had had one miscarriage previously, but had failed to conceive for the last seven years. Her husband's semen contained 308,000,000 moving cells in the total ejaculate. The patency of the wife's Fallopian tubes was proved by uterosalpingography.

The details of the ovulation timing appear in Table IX.

TABLE IX. CASE 9

OVULATION TESTS	MENSTRUAL CYCLE		COMMENTS
	OVULATION ON CYCLE DAY	LENGTH IN DAYS	
1	8	24	Control month
2	9	--	Coitus on ovulation cycle day. Conception followed

The menstrual cycles of this patient were quite regular, and her ovulation reaction during the control month was normal, occurring on day 8 of her cycle.

Conception occurred during the first test month on the fifth day of the rat color reaction which was cycle day 9.

CASE 10.—Patient married for six years with failure of conception to occur for one and one-half years. Wife Rh negative, husband Rh positive. Husband relatively infertile for several months in the early months of ovulation timing, but judged to be fertile in the remainder of the ovulation timing period. Patency of wife's left Fallopian tube confirmed by uterosalpingography. Patency of right tube equivocal.

The details of the ovulation timing appear in Table X.

TABLE X. CASE 10

OVULATION TESTS	MENSTRUAL CYCLE		COMMENTS
	OVULATION ON CYCLE DAY	LENGTH IN DAYS	
1	16	28	Coitus days 15 and 16. Sperm count 77 million
2	13	27	Coitus days 13 and 14. Still low sperm count
3	Abnormal	28	Coitus days 13, 14
4	Abnormal	31	Coitus day 12
5	13	26	Coitus days 13 and 14
6	12	26	Coitus days 11, 12, 13
7	13	28	Insemination day 13. Coitus day 14
8	12	26	Insemination day 13. Prediction—no conception
9	13	26	Coitus days 13, 14, 15
10	14	26	Coitus day 14
11	11	--	Intrauterine insemination day 11. Conception followed

Ovulation was timed for ten months before conception took place during the eleventh month. The 10 failures are explained on the following grounds. Tests 1 and 2, husband infertile. Tests 3 and 4, ovulation reactions abnormal.

Tests 5, 6 and 7, no explanation available. It is possible that an error in the technique of the insemination can have accounted for the failure in test month 7. Test 8 failure due to fact that insemination was performed after ovulation had taken place. No conception was predicted. At this point, uterosalpingography was performed, which revealed the possible blockage of the right Fallopian tube, which blocking may have been released by the oil employed in the test. The failures in test months 9 and 10 are not explained, unless sperm fail to reach the inside of the uterus.

The successful impregnation followed intrauterine insemination on day 11 of the cycle which was the fourth day of a normal rat color reaction.

Discussion

The present group of observations includes ones upon couples who were studied at various times while the rat test was being developed. It is believed that conception would have taken place earlier in some instances, if as much had been known in the beginning of the study as was known by the time that the last of the present series of patients was investigated.

A total of 47 tests for ovulation was made. Seven control month tests were carried out. Attempts at conception were advised against during these months.

Fourteen tests revealed the presence of abnormal ovulation reactions. Previous experience had indicated that conception will not occcur in the presence of such reactions. That observation was confirmed in the present series of patients, where coitus was practiced.

The remaining 26 tests registered normal ovulation reactions. Conception should have occurred in association with the first normal reaction of each patient had all conditions been favorable. Eleven conceptions did take place.

There were 15 failures of which four cannot be explained. Three were due to male infertility, and 11 failures are explained as follows: six resulted from the fact that coitus was practiced on the day immediately preceding the day of ovulation. Coitus on the day prior to ovulation has the probable effect of reducing the sperm count to a point where the male is infertile on the day of ovulation, especially in the case of males of relatively low fertility.

Two other failures can be explained on the ground that coitus did not occur until the day after ovulation. It was advised that intercourse take place at this time in these two instances, in order to check the hypothesis that conception would be unlikely or impossible at this time.

The rat ovulation test appears to have a very definite place in the treatment of the sterile couple. If the urine of the patient does not produce any response in the rat ovary during any month that she is tested, her chance of becoming pregnant is very slight.

Some women, tested during many consecutive months, exhibited few normal ovulation reactions. Knowledge of this state of affairs aids greatly in evaluating their chances of becoming pregnant. It emphasizes the need for testing such women every month in order to discover the few times that they may conceive in any long period of time.

The majority of women ovulate normally each month. When this fact has been established by several tests, it then becomes possible to predict the date of

succeeding ovulations, without the necessity of testing each succeeding month for the exact day.

The rat ovulation test has still another important value. It provides knowledge of the day of ovulation prior to the event, and the nature of the reaction is such that it gives two or three days of warning previous to the impending ovulation. This warning is of special value in those cases in which artificial insemination appears to be a necessity, since it allows time for preparation for this procedure. An additional value of the test lies in the fact that it makes unnecessary the carrying out of an endometrial biopsy.

Still another advantage in the use of the rat ovulation test lies in the fact that advance knowledge of the day of ovulation makes it possible to have the husband conserve his sperm cells for that day. In cases where the sperm cells of an anonymous donor are to be employed, knowledge of the exact day of ovulation makes it possible to be economical in the use of such donor specimens.

Summary

1. Conceptions are reported in nine relatively infertile and in one highly fertile woman, aided by the use of the rat ovulation test for the purpose of timing either coitus or artificial insemination with the day of ovulation.

2. The use of the method is described, and some of its advantages are outlined.

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PREGNANCY COMPLICATING TUBERCULOSIS

A Survey for an Eleven-Year Period*

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IN AN eleven-year period from January, 1930, to January, 1941, there have been 28,846 patients delivered at the Elizabeth Steel Magee Hospital. This included 103 cases of known pulmonary tuberculosis—an incidence of 0.35 per cent. Clinical surveys for a 5- to 15-year period were available for 62 tuberculous patients. The records of the remaining 41 patients were considered too incomplete to include in this report.

The various extremes from termination of the pregnancy in the first trimester to allowing the pregnancy to go to term were employed in the management of pregnancy in these 62 patients. Abortions were recommended by medical consultants in 24 patients. Twelve patients were delivered by cesarean section, and 26 patients delivered spontaneously. In the majority of the 24 patients aborted, medical consultants recommended sterilization. During this survey period the management of pregnancy complicated by tuberculosis has shown a conservative swing from early termination to spontaneous delivery at term. The grade of tuberculosis varied from arrested cases to far-advanced involvement (Fig. 1).

This survey was composed of 24 primiparas and 38 multiparas. They varied between the ages of 19 and 44 years. Our survey period in these patients varied from 5 to 15 years.

Of the 24 primiparas, pregnancies were terminated within the first trimester in 10, five were delivered by cesarean section; 13 of these patients being sterilized at the time of operation. The remaining nine patients were delivered spontaneously. The second pregnancy in one patient that delivered spontaneously was terminated by cesarean section, and she was sterilized at the time of operation. Sterilization following 1 cesarean section failed, and the second pregnancy was terminated within the first trimester and the patient was resterilized.

Of the 38 multiparas, 16 were delivered spontaneously. In one patient that had had two spontaneous births, the two pregnancies which followed were terminated by cesarean section, sterilization having failed following the first cesarean delivery. Seven patients were delivered by cesarean section and sterilized, and the pregnancies in 15 patients were terminated within the first trimester. In two of the 15 patients aborted therapeutic abortions were performed without sterilization. Two sterilizations failed among the group of 13 patients aborted and sterilized. One patient was allowed to go to term and she

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was delivered by cesarean section and resterilized. The pregnancy in the second patient was terminated within the first trimester of gestation.

The 62 patients in this survey gave birth to 149 viable infants. This included 89 infants delivered after the diagnosis of tuberculosis. There were four premature infants, including one set of twins. The fetal mortality was 1.34 per cent (two deaths). One baby died of intracranial hemorrhage, and the second infant died of prematurity following a cesarean section done in the seventh month of pregnancy because of a fulminating pre-eclampsia.

Inactive Tuberculosis

There were seven patients in this group. All of these patients are living. Four were primiparas and three were multiparas.

All of the primiparas were delivered spontaneously and, on last report, ranging from five to eleven years since their first pregnancy, physical examination, laboratory studies, and serial x-rays of their chests showed the tuberculosis to be inactive. The length of time between the diagnosis of tuberculosis and their first pregnancy ranged from four to eleven years. These patients have since given birth to a total of eight infants. One of these infants was delivered by cesarean section because of a fulminating pre-eclampsia at seven months resulting in a stillborn child.

Two of the three multiparas were delivered spontaneously. The pregnancy was terminated within the first trimester in the third patient, and she was also sterilized because of epilepsy. She had had two term, spontaneous deliveries before the diagnosis of tuberculosis. The other two multiparas gave birth to a total of five term infants after the diagnosis of tuberculosis was made. In one of these patients there was a term delivery one year after the diagnosis of tuberculosis, and on the twenty-fifth postpartum day she had a pulmonary hemorrhage, but on x-ray examination there was no evidence of gross active tuberculosis. Five years later there was questionable activity of the tuberculosis following delivery. With her last pregnancy, four years later, the tuberculosis was considered inactive.

In all of these patients, primiparas and multiparas, pregnancy did not reactivate a tuberculous process which had been considered as inactive.

Quiescent or Latent Tuberculosis

Five patients had quiescent or latent tuberculosis at the time of their first admission to the hospital. There were three primiparas and two multiparas in this group. All of the patients are living and well.

Two primiparas were delivered by cesarean section. In one patient a diagnosis of moderately advanced tuberculosis with a positive sputum was made eight years before her first pregnancy. The second patient became pregnant four years after a diagnosis of tuberculosis. At that time the tuberculosis was considered as moderately advanced. She received active therapy for four years. A cesarean section was done because of a premature separation of the placenta.

Six years later both patients were considered as having no evidence of active tuberculosis. Within this interval of time they both gave birth to another term infant by cesarean section. In the third primipara a diagnosis of quiescent tuberculosis was made three years before her pregnancy. The pregnancy was terminated within the first trimester, and the patient was sterilized.

The first multipara was delivered spontaneously of two term infants. The diagnosis of tuberculosis was made during her first pregnancy. The second multipara had four term infants. Her case history is presented.

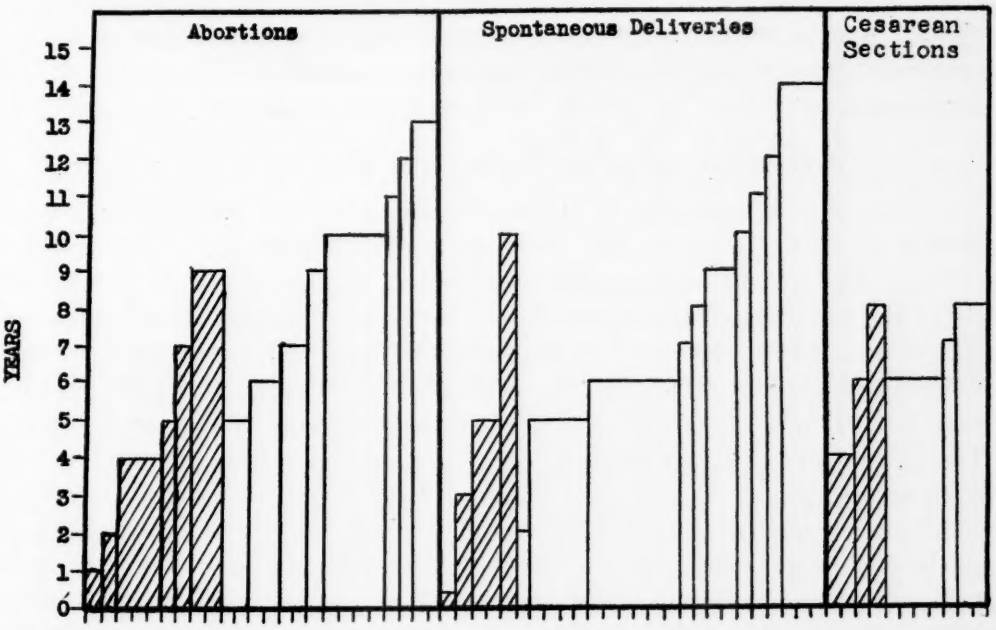

Fig. 1.—Length of study of the various patients in the survey. The mortality is represented by the shaded portions in the chart. Twenty-five patients were aborted; there were nine deaths. There were 26 spontaneous deliveries with five deaths; one patient is listed whose prognosis is poor. There were 11 cesarean sections, with four deaths. One patient was not included in this chart because of death due to a postoperative complication during a thoracoplasty operation. One patient, though followed for ten years, died of a syphilitic infection and has not been included in the final mortality figures. Only deaths directly due to tuberculosis were considered in the final results.

Case 1.—D. S., a gravida ii, 25 years of age, white, was admitted to the hospital Aug. 15, 1937, with a pregnancy at term and a diagnosis of quiescent tuberculosis. She was delivered spontaneously, and her postpartum course was uneventful. Her tuberculosis was diagnosed as moderately advanced in 1931. She was admitted to the sanatorium at that time for stabilization of her pneumothorax and phrenectomy. The pneumothorax therapy was discontinued in 1932 because of an obliterative pleurisy. At that time the tuberculosis was considered as far advanced. On Jan. 29, 1934, the patient was readmitted and a thoracoplasty was done; the patient was discharged Nov. 24, 1934. A tonsillectomy was done in 1935. The patient became pregnant in 1936 and gave birth spontaneously to a term infant that same year. The following year she again became pregnant and was delivered spontaneously. Six months later (Feb. 17, 1938) her condition was considered as good, and on x-ray examination there was almost complete collapse of the left lung; her sputum was negative. She again became pregnant, and on Jan. 15, 1939, she was delivered by low cervical cesarean

section and sterilized. On x-ray examination April 20, 1940, there was scattered right upper tuberculosis of minimal extent; her sputum was negative. In 1941 the patient again became pregnant and was delivered at term by cesarean section and resterilized. On x-ray examination Oct. 29, 1942, there was scattered nodular and linear involvement of the right upper lung field with complete collapse of the left lung. On April 20, 1945, the tuberculosis was considered as apparently arrested, and at present the patient is doing well and does all of her own housework.

It is interesting to note that this last patient had far-advanced tuberculosis which was treated by thoracoplasty after pneumothorax and phrenectomy had failed. She had four pregnancies following this. Two pregnancies were terminated by cesarean section. The postpartum and postoperative courses in all of these deliveries were uneventful. There was no reactivity of the tuberculosis.

Unilateral Active Apical or Minimal and Aberrative Tuberculosis

There were 10 patients in this group. Four were primiparas and six were multiparas. One patient is dead—an incidence of 10.0 per cent.

The four primiparas were all considered as arrested cases of tuberculosis six to ten years after their first pregnancy. In one primipara the pregnancy was terminated within the first trimester, but she was not sterilized. Her tuberculosis was also diagnosed five years before her pregnancy. During a six-year interval this same patient gave birth spontaneously to two term infants. The third primipara was delivered by cesarean section and sterilized. The cesarean section was done because of a cephalopelvic disproportion. The tuberculosis was diagnosed during the pregnancy. There was no acute exacerbation of the disease following delivery. In the fourth patient it was evident that the tuberculosis was probably activated by her first pregnancy which terminated spontaneously. However, the tuberculosis was considered as minimal and there was no evidence of activity following her second pregnancy which occurred one year later. Her complete history follows:

CASE 2.—M. E., a gravida i, 27 years of age, white, was admitted to the hospital Jan. 4, 1937. She was at term and was delivered spontaneously. She was discharged Jan. 14, 1937, after an uneventful postpartum course. One month later she was readmitted to the hospital complaining of pain in her chest and cough. She had been having frequent chills and night sweats. She was diagnosed as having a pleural effusion, and this was proved as tuberculous in origin by guinea pig injection. She remained febrile and was finally discharged May 5, 1937, and sent to a tuberculosis sanatorium. The effusion completely disappeared, and she was discharged from the sanatorium on Oct. 19, 1937. When seen six months later she was feeling well and gaining weight; her sputum was negative. On x-ray examination Feb. 4, 1938, there was slight tuberculous involvement of the left second interspace. The patient was next seen July 8, 1938; she was 3½ months pregnant and refused to be aborted and sterilized. She was delivered by low cervical cesarean section and sterilized Jan. 20, 1939. Eight months later there was no evidence of active tuberculosis on routine examination. On re-examination March 6, 1942, there was no evidence of tuberculous activity. At present the patient is well and working.

Five of the six multiparas are living and well, and on last routine examination there was no evidence of tuberculous activity. The sixth patient was a gravida iii. Two term pregnancies had occurred before the diagnosis of tuberculosis. The third pregnancy was a spontaneous aseptic abortion at three months' gestation. Two years after this abortion the patient was bedfast with miliary tuberculosis and died the following year. Of the five multiparas that are living, one was delivered by cesarean section because of a pelvic deformity. A diagnosis of tuberculosis of the right hip was made thirteen years before. One year after her pregnancy there was minimal tuberculosis in her right lung. Six years later the patient had no evident active tuberculosis, and in this interval she again gave birth to a term infant by cesarean section. Termination of the pregnancy within the first trimester was done in three of the remaining four multiparas. Two of these patients had one or more term pregnancies before the diagnosis of tuberculosis. In one patient the diagnosis was made during her last pregnancy; in the other, the diagnosis of tuberculosis was made after her second pregnancy, and she received one year of pneumothorax therapy before her third and last pregnancy. The third patient had two spontaneous aseptic abortions before the diagnosis of tuberculosis was made and two abortions followed. The fourth multipara had three term spontaneous deliveries. The last pregnancy occurred after the diagnosis of tuberculosis. Four to ten years after their last pregnancy all four multiparas showed no evidence of tuberculous activity.

Moderately Advanced Inactive Tuberculosis

Two patients had moderately advanced inactive tuberculosis. One patient died of probable intestinal tuberculosis. No autopsy was obtainable.

CASE 3.—L. L., a gravida ii, 27 years of age, Negro, was admitted to the hospital Oct. 25, 1940, with a diagnosis of inactive moderately advanced tuberculosis and a pregnancy at term. She was delivered spontaneously. Early in her postpartum period she developed a febrile course with a temperature as high as 104° F. The patient had no respiratory signs or symptoms. On Dec. 6, 1940, the patient developed large cervical nodes which were proved to be tuberculous in origin. The patient was admitted to the sanatorium Dec. 15, 1940, and was discharged nine months later. At no time was there a positive sputum or evidence of tuberculous activity in the chest. On re-examination June 13, 1943, three years later, there were suggestive findings in the chest of active tuberculosis. When seen 10 months later the patient was gaining weight and doing well. On June 15, 1945, the patient complained of persistent diarrhea and had lost considerable weight. There was no significant tuberculosis in the chest, and the sputum was negative. The patient died three months later of probable intestinal tuberculosis.

Reactivation of a latent tuberculous process is very suggestive in this case because of the febrile postpartum course and the enlarged cervical nodes. The disappearance of the tuberculous process for approximately five years accounts for the probable diagnosis of intestinal tuberculosis for the cause of death which was suggestive by the clinical symptoms of diarrhea and marked loss in weight.

Acute Active Tuberculosis

There was one patient diagnosed as having acute active tuberculosis. She died one year later following a therapeutic abortion and sterilization.

Case 4.—I. W., a gravida iii, 23 years of age, white, was admitted March 1, 1935, with a diagnosis of acute active tuberculosis. She was three months' pregnant, and the tuberculosis had been diagnosed during this pregnancy. Her previous two pregnancies were term, spontaneous deliveries—the last of which terminated three years before the present pregnancy. The pregnancy was terminated and the patient sterilized, and she was discharged March 28, 1935. She was immediately admitted to the sanatorium and died July 25, 1936.

Unilateral Moderately Advanced Tuberculosis

One patient had unilateral moderately advanced pulmonary tuberculosis. She was a gravida ii. The first pregnancy terminated spontaneously at term and occurred before the diagnosis of tuberculosis. A diagnosis of tuberculosis was made the following year, and three years later it was described by x-ray as advanced active tuberculosis. A thoracoplasty was done at that time. Two years later the patient again became pregnant. The pregnancy was terminated within the first trimester by x-ray induction which resulted in eventual sterilization. At the time of her second pregnancy there was marked fibrosis of the collapsed lung with no extension to the left lung.

Bilateral Moderately Advanced Tuberculosis

There were 19 patients in this group. Five patients were primiparas, and the remaining 14 were multiparas. The mortality was 26.4 per cent (five patients). In six patients the pregnancy was terminated in the first trimester by surgical means; in one patient the pregnancy was terminated in the first trimester but she was not sterilized. Three patients were delivered by cesarean section and the remaining nine were delivered spontaneously, of which one was sterilized on the tenth postpartum day.

One primipara had a complicating pre-eclampsia. Her membranes were ruptured artificially in the eighth month of pregnancy, and she was delivered spontaneously after a short labor. Her tuberculosis had been diagnosed three years previously. Following the diagnosis of tuberculosis the patient was hospitalized for six months. She received a total of eight months of pneumothorax therapy. The second primipara had a multiple pregnancy. She was delivered prematurely of viable twins at seven one-half months. She was then sterilized on the tenth postpartum day. Her tuberculosis had been diagnosed one year before her pregnancy. The third primipara was aborted and sterilized. Her tuberculosis had been diagnosed a few months before her pregnancy. The remaining two primiparas were aborted and sterilized. All five patients are living and well six to thirteen years after their last pregnancy, and on routine examination the tuberculosis was described as arrested.

In two of the five multiparas that died, pregnancy was terminated and sterilization done within the first trimester. They each had had one to four term spontaneous deliveries before the diagnosis of tuberculosis had been made.

The multipara that had one term pregnancy before the diagnosis of tuberculosis developed tuberculous peritonitis seven years after her abortion and died within two years. The tuberculosis had been diagnosed shortly after her first pregnancy. The other multipara was found to have tuberculosis after her fourth spontaneous delivery had occurred. She received pneumothorax therapy but remained ambulatory. Three years later she again became pregnant, and this was terminated at three months' gestation. At the time of her abortion, the tuberculosis was considered as quiescent. Four years later the patient died of far-advanced tuberculosis. The third multipara, a gravida vii, was found to have tuberculosis during her last pregnancy. She was delivered spontaneously and died ten years later of far-advanced pulmonary tuberculosis. The fourth multipara was delivered by cesarean section and sterilized. Her first pregnancy was a spontaneous term delivery, and tuberculosis was diagnosed one year later. Two years after the diagnosis of tuberculosis the disease was considered as arrested. The following year she developed a positive sputum and was hospitalized for ten months. When discharged from the sanatorium the tuberculosis was again considered as arrested. The fifth patient died six years after the diagnosis of tuberculosis. Her case history is presented.

CASE 5.—G. B., a gravida iv, 36 years of age, white, was admitted to the hospital Aug. 26, 1940, with a diagnosis of moderately advanced active tuberculosis with a guarded prognosis and pregnancy at term. The tuberculosis was first diagnosed in 1939. On x-ray examination June 1, 1940, there was extensive bilateral involvement. The patient was seven months pregnant at the time. Cesarean section and sterilization were recommended. The patient delivered spontaneously and was discharged Sept. 5, 1940, after an uneventful postpartum course. On x-ray examination of the chest on Nov. 18, 1940, there was extensive bilateral involvement but to no greater extent than in the previous x-ray examination taken when the patient was seven months pregnant. On Oct. 10, 1942, the prognosis was poor; the patient was losing weight and complaining of generalized chest pain. An x-ray taken Jan. 7, 1944, showed extensive tuberculous cavitation, and six months later the patient was hospitalized. She died May 12, 1945, of far-advanced tuberculosis.

The diagnosis of tuberculosis in this last patient was made during her fourth pregnancy. X-ray examinations made four months following delivery showed no further extent of the disease. The tuberculosis gradually progressed over a period of five years, terminating in death.

The remaining nine multiparas are living. The first patient was a gravida viii. She was delivered spontaneously. Six term pregnancies had occurred before the diagnosis of tuberculosis was made. Her initial diagnosis was made eight months after her sixth pregnancy. Two years later, there was minimal chest activity present. In this interval she gave birth to one term infant. During the five years that followed she again gave birth to another term infant. On last report her tuberculosis was considered as inactive. The second patient had stationary bilateral tuberculosis two years after her last pregnancy. She was a gravida v with three term pregnancies occurring after the diagnosis of tuberculosis. The third patient was a gravida iii. All pregnancies occurred

three years after the diagnosis of tuberculosis had been made. Seven years later she was diagnosed as having moderately advanced tuberculosis of the fibroid type. The fourth patient was diagnosed as having far-advanced tuberculosis five years after her last delivery. She was a gravida viii and seven pregnancies had occurred before the diagnosis of tuberculosis. Her husband had died four months before the termination of her last pregnancy of far-advanced active pulmonary tuberculosis. The fifth patient was a gravida v. She was delivered spontaneously at term. She had had three term pregnancies previous to the diagnosis of tuberculosis. Eight years later she was diagnosed as having quiescent moderately advanced tuberculosis of the fibroid type. The sixth patient was delivered spontaneously. Three term pregnancies had occurred before the diagnosis of tuberculosis and three term pregnancies followed. Upon re-examination fourteen years after the diagnosis of tuberculosis, tuberculosis of the cirrhotic type was found. The following year the patient was readmitted to the sanatorium for further treatment. The seventh patient was delivered by cesarean section three years after the diagnosis of tuberculosis. One term pregnancy had occurred five years before this diagnosis. One year following the cesarean section and sterilization the patient again became pregnant and the pregnancy was terminated within the first trimester of gestation and she was resterilized. Ten years later the prognosis was still guarded and the patient is on a limited routine. The eighth patient was a gravida iv. Tuberculosis was diagnosed a few months after her third spontaneous delivery. Her last pregnancy was terminated within the first trimester. At present the prognosis is still guarded and the patient rests two hours daily. The case history of the ninth multipara is presented.

CASE 6.—M. K., a gravida ii, 23 years of age, white, was admitted Jan. 7, 1940, with a diagnosis of tuberculosis moderately advanced, prognosis guarded, and inevitable abortion. In 1933 the right kidney had been removed because of tuberculosis. On Feb. 16, 1939, she was diagnosed as having pleurisy with effusion, and on x-ray examination there was tuberculous involvement of the right lung base. The patient became pregnant and the pregnancy was terminated at three months; her postoperative course being complicated by pneumonia and pleurisy. The patient was discharged Jan. 20, 1940, following a febrile postpartum course. This was followed by a gradual loss in weight and malaise. On x-ray examination, May 24, 1940, there was evidence of right upper tuberculosis with extensive pleuritis and fibrosis. On Jan. 17, 1941, the patient was again diagnosed as pregnant and a therapeutic abortion was done. On Feb. 6, 1942, the patient complained of a persistent cough and there were extensive fine râles in the left apex; she was advised not to become pregnant. On May 15, 1942, she was again diagnosed as three months pregnant and on x-ray examination there were small areas of involvement in the right apex and base. On x-ray examination Oct. 20, 1942, there was central cavitation with extensive hilar involvement of the right lung. On Nov. 12, 1942, the patient was delivered spontaneously. The pregnancy was complicated by a breech presentation. On April 1, 1943, there were no signs or symptoms of active tuberculosis. The patient again became pregnant and miscarried Sept. 9, 1943. On Sept. 24, 1943, there were no signs or symptoms of active tuberculosis and on x-ray examination the tuberculosis was considered as stable. On Jan. 17, 1944, routine examination showed inactive disease. At present the tuberculosis is considered as arrested.

Advanced Tuberculosis

Sixteen patients had advanced pulmonary tuberculosis or advanced tuberculosis with involvement of the larynx or pharynx. There were seven primiparas and nine multiparas in this group. Eleven patients are dead.

Eighty-five per cent of the patients in whom the pregnancies were terminated within the first trimester of gestation died, as compared to 62.5 per cent of the patients who went to term. If we compared the patients who delivered spontaneously with those delivered by cesarean section, four delivered spontaneously and two died, as compared to three out of four patients who were delivered by cesarean section.

Two primiparas were aborted and sterilized, and one delivered spontaneously. The first patient that was aborted and sterilized had far-advanced tuberculosis, the diagnosis being made one year before her pregnancy. She died seven years later. The second primipara was diagnosed as having advanced bilateral pulmonary tuberculosis with laryngeal and pharyngeal involvement. She became pregnant four years later and was aborted and sterilized, and died four years later. The third primipara delivered spontaneously. She had far-advanced pulmonary and renal tuberculosis which was diagnosed during her pregnancy and died three years later. The fourth primipara was delivered by cesarean section and sterilized. Her tuberculosis was diagnosed as moderately advanced four years before. Two years after the cesarean section the patient again became pregnant and the pregnancy was terminated within the first trimester and the patient was re-sterilized. She died of far-advanced tuberculosis five years later. The fifth patient delivered spontaneously and expired on the fifth postpartum day. Her case is presented.

Case 7.—M. S., a gravida i, 19 years old, white, was admitted to the hospital July 3, 1935, with a diagnosis of far-advanced, active tuberculosis with laryngeal and pharyngeal involvement. She was seven months pregnant. One year before admission she began to lose weight, developed a cough, slight temperature, night sweats, and hemoptysis. During the first half of her pregnancy she became hoarse and had difficulty in swallowing. She gave birth prematurely to a seven months' stillborn infant after a short uncomplicated labor. There was a rapid generalized failure following delivery, and the patient expired on the fifth postpartum day.

The remaining two primiparas are on a limited routine nine and eleven years, respectively, after the diagnosis of tuberculosis. One patient became pregnant one year after the diagnosis of tuberculosis and she was delivered at term by cesarean section and sterilized. The pregnancy in the other patient occurred four years after the diagnosis of tuberculosis, and it was terminated within the first trimester and the patient was sterilized.

All nine multiparas had far-advanced pulmonary tuberculosis. Two patients had two to five pregnancies before the diagnosis of tuberculosis. In both of these patients the pregnancy was terminated within the first trimester and one was sterilized. One patient died nine years after her last pregnancy. The other patient was diagnosed as having moderately advanced bilateral tuberculosis

of the caseopneumonic type five years later. Two years previous to her last pregnancy she was hospitalized for five months, at which time a phrenectomy was done. The third patient was delivered by cesarean section. She was a gravida ii. Both pregnancies occurred after the diagnosis of tuberculosis. The first pregnancy was a spontaneous birth. She died four years after her last delivery. Two of the remaining six multiparas are living and well ten to fourteen years after the diagnosis of tuberculosis. Both cases are presented.

CASE 8.—L. S., a gravida ii, 24 years old, Negro, was admitted July 12, 1933, with a diagnosis of bilateral moderately advanced tuberculosis with cavitation, prognosis poor. She was at term and was delivered spontaneously, and was discharged July 27, 1933. Her postpartum course was complicated by a low-grade temperature and secondary anemia. Her tuberculosis was diagnosed during this pregnancy. She refused sanatorial care and was next seen Sept. 18, 1935, at which time she was diagnosed as having advanced tuberculosis with large cavitations. On Oct. 31, 1941, she gave birth spontaneously to a term infant and was sterilized on the tenth postpartum day. On x-ray examination two months after the last delivery there was scattered bilateral tuberculosis of moderate density with extensive fibrosis. On re-examination of the chest March 11, 1943, there was extensive bilateral tuberculosis with moderate fibrosis. The sputum was negative. The fibrosis was much more marked on x-ray examination of the chest June 12, 1944. On March 5, 1945, there were occasional râles and no symptoms of tuberculosis. On last examination May 6, 1946, she had symptoms of activity as verified by routine examination.

CASE 9.—H. M., a gravida ii, 27 years old, white, was admitted to the hospital Dec. 25, 1936, with a diagnosis of bilateral tuberculosis with a poor prognosis, eclampsia, and eight months' pregnancy. She developed convulsions the day before admission. On admission her blood pressure was 168/120. There was a 4 plus albuminuria. Membranes were ruptured artificially Dec. 29, 1936, and five and one-half hours later she gave birth spontaneously to a viable infant. The day preceding delivery she developed a fibrinous pleurisy. She was discharged from the hospital Jan. 17, 1937. Her tuberculosis had been diagnosed in 1932. She was hospitalized for three years. On x-ray examination June 13, 1935, there was scattered involvement of the right second and third interspaces with gross left lung tuberculosis. On May 8, 1936, there was a gross effusion of the left side of the chest. She was diagnosed as pregnant Sept. 10, 1936, but refused to be aborted and sterilized. Bed rest was advised, and the pregnancy was to be terminated by cesarean section. Re-examination of her chest four months after delivery showed no further extension of the disease. Nov. 12, 1937, she was seen, and she complained of nervousness and marked loss of weight. Her basal metabolic rate was found to be plus 50. A subtotal thyroidectomy was done March 5, 1938. X-ray of her chest was taken Oct. 21, 1938, and showed marked fibrosis; her sputum was negative and she was gaining weight. On x-ray of her chest May 16, 1941, there was extensive old right upper tuberculosis with gross left lung tuberculosis and marked pleural thickening with mediastinal detrusion. On June 18, 1943, the x-ray findings were essentially the same; her basal metabolic rate had risen to plus 30. On her last examination May 9, 1945, there was marked cirrhotic involvement of the left lung. At present the patient is doing well and is on a limited routine.

One multipara that was aborted and sterilized died five years later during a thoracoplasty operation. Three term pregnancies had occurred before the diagnosis of tuberculosis. The remaining three multiparas are dead. Two were

delivered by cesarean section and sterilized, and died four to eight years after their last pregnancies. The last patient was aborted and sterilized and died four years after the diagnosis of far-advanced tuberculosis. Two term spontaneous deliveries had occurred within this interval of time.

Tuberculosis With Death Due to Other Causes

One multipara had unilateral active tuberculosis complicated by tertiary syphilis. She was a gravida vi and all pregnancies occurred after the diagnosis of tuberculosis. She died ten years later of tertiary syphilis as determined by autopsy findings, and was therefore not included in the final mortalities.

Management of Pregnancy

The conservative management of the pregnancy consisted in allowing the patient to go to term and to deliver spontaneously. Her antepartum care was augmented by careful management of the tuberculosis. This consisted in sanatorial care when needed and closely supervised ambulatory treatment. Anesthesia during delivery was limited to nitrous-oxide and oxygen supplemented with a pudendal block or low spinal anesthesia. The second stage of labor was shortened by resorting to low forceps delivery. All laparotomies performed either for cesarean section delivery of the patient or to abort and sterilize the patient were done under spinal anesthesia.

Discussion

Clinical studies for a period of five to fifteen years were made in 62 patients. The gross mortality was 33.8 per cent (21 deaths). The corrected final mortality was 30.6 per cent. Two deaths were excluded because one death was due to tertiary syphilis and the other death was due to generalized collapse during the fourth stage of a thoracoplasty operation. The mortality for the primiparas was 21 per cent, and the mortality for the multiparas was 32.5 per cent. Twenty-six patients delivered spontaneously with a mortality of 19.2 per cent. There were 11 cesarean sections with a mortality of 36.3 per cent, and the mortality was 38.5 per cent in 25 patients in whom therapeutic abortions were performed. This variation in mortality impresses one in the assumption that operative interference is associated with the greatest mortality (Table I).

TABLE I. INCIDENCE OF ADVANCED DISEASE WITH MORTALITY BETWEEN VARIOUS TYPES OF DELIVERIES

	ABORTED	SPONTANEOUS	CESAREANS
Primiparas			
Moderately or advanced active	77.7%	50.0%	50.0%
Mortality	28.6%	50.0%	-----
Multiparas			
Moderately or advanced active	68.8%	66.6%	44.4%
Mortality	63.6%	25.0%	100.0%
Combined results—			
Primiparas and multiparas			
Moderately or advanced active	73.3%	53.3%	47.2%
Mortality	43.1%	37.5%	50.0%

The above results are based on the final analysis of the patients and not on first admissions.

On first admission there were 24 primiparas. Thirty-seven per cent of these patients became pregnant for the second time or more; 11.2 per cent of the patients that had more than one pregnancy are dead; 13.3 per cent of the patients with only one pregnancy are dead.

Eight primiparas delivered spontaneously with a mortality of 22.2 per cent. Two primiparas were delivered by cesarean section with no mortality, and in nine patients therapeutic abortions were performed, with a mortality of 22.2 per cent. If we classify these primiparas according to the extent of the tuberculosis, 50 per cent of the patients that were delivered spontaneously had moderately advanced active or far-advanced active tuberculosis. Fifty per cent of the patients that were delivered by cesarean section are also in this same classification, and 77.5 per cent of the patients in whom therapeutic abortion had been performed had advanced or moderately advanced active pulmonary tuberculosis. It is also noted that the age group for the primiparas varied from nineteen to thirty-eight years, and the four patients who died were in the age group from nineteen to twenty-one years. This is the age group wherein the highest mortality in tuberculosis occurs. If we consider the management of the pregnancy in these four patients, two patients were aborted and the remaining two delivered spontaneously. The two who delivered spontaneously had far-advanced pulmonary tuberculosis complicated by either renal or laryngeal and pharyngeal tuberculosis. The two patients who were aborted had far-advanced tuberculosis or tuberculosis complicated by laryngeal or pharyngeal involvement.

Eighteen multiparas delivered spontaneously, with a mortality rate of 16.6 per cent. Nine patients delivered by cesarean section with a mortality of 44.7 per cent. In 16 patients the pregnancies were terminated within the first trimester, with a mortality of 50 per cent. If we classify the multiparas according to the extent of the disease, 66.6 per cent of the patients who were delivered spontaneously had bilateral moderately advanced or far-advanced active tuberculosis; 44.4 per cent of the patients who were delivered by cesarean section were also in the above classification, and 100 per cent of the patients are dead; 62.5 per cent of the patients in whom therapeutic abortions were performed also had bilateral advanced or moderately advanced active tuberculosis. The age group for the multiparas varied from 23 to 44 years of age, and more deaths occurred between the ages of 23 and 30 than between the ages of 31 and 45 years.

Summary and Conclusions

1. A review of 62 tuberculous patients with a complicating pregnancy is presented.

2. The known incidence of tuberculosis complicating pregnancy at the Elizabeth Steel Magee Hospital is 0.35 per cent.

3. The final gross mortality in this survey was 33.8 per cent, and the corrected final mortality was 30.6 per cent.

4. The mortality for the patients who delivered spontaneously was 19.2 per cent.

5. The mortality for the patients who delivered by cesarean section was 36.3 per cent.

6. The mortality for the tuberculous patients in whom the pregnancy was terminated within the first trimester was 38.5 per cent.

7. Sixty-one and five tenths per cent of the 62 patients had moderately advanced or far-advanced active tuberculosis; 44.8 per cent of these patients are dead. This included all types of deliveries including therapeutic abortions.

8. The best results in this survey were obtained in those patients who were delivered spontaneously regardless of the extent of the tuberculosis.

9. To determine tuberculous activity, physical examination, laboratory studies, including blood sedimentation rates, and serial x-rays are necessary.

DILUTE SOLUTION, CATHETER, CONTINUOUS SPINAL ANALGESIA FOR LABOR AND DELIVERY*

A Preliminary Report

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IN OCTOBER, 1944, the first dilute solution continuous spinal anesthetic for labor and delivery was administered by one of us (S. M. S.) using a malleable needle and a needle shield so that the patient could lie on her back in her own bed during labor. This work was reported in an earlier issue of this JOURNAL.[1]

On the basis of the contribution which Tuohy[2] made in introducing a ureteral catheter into the subarachnoid for anesthetic purposes, it was decided to continue dilute solution spinal analgesia for labor and delivery utilizing the catheter rather than the malleable needle and shield. We observed that the catheter technique offered more advantages and permitted greater control than the needle shield method.

The dilute solution approach toward the control of pain during labor and delivery was investigated in order to overcome some of the complications of continuous caudal analgesia such as: increased operative forceps deliveries, toxic reactions to the mother and fetus due to large amounts of anesthetic drugs, the imminence of massive spinal anesthesia should the epidural solution suddenly find its way into the subarachnoid space, the necessity for constant observation of the parturient, difficulty in inserting the needle, and the potentiality of infection in an extensively contaminated area.[3]

Continuous spinal analgesia for labor and delivery has been utilized by others such as Hinebaugh and Lang, Ebner and Lull, and Hingson. These workers, however, did not use extremely dilute anesthetic solutions which exert neither a somatic sensory nor a motor effect; and further, they were unable to permit the patient to lie on her back because of the indwelling needle, and withdrew the needle before transporting the patient to the delivery room. This technique did not gain much popularity because of persistent unilateral analgesia, paralysis of motor nerves, the anesthetic solution ascending to undesirable heights in the subarachnoid space, causing the blood pressure to fall to shock levels, interfering with uterine contractions, and subsequently retarding the normal progress of labor.

We have overcome the complications of continuous caudal analgesia and the undesirable features of spinal analgesia, as used in the past, by injecting into

*Presented before the First Annual Staff Meeting of the South Baltimore General Hospital on Jan. 8, 1947.

the subarachnoid space through a ureteral catheter an anesthetic solution which is so dilute that *no somatic sensory effect could be detected, and little or no motor paralysis involving the musculature of the thorax, abdomen, or extremities was produced; yet, the pain of labor contractions were abolished.*

Pains from the contracting uterus have been successfully abolished with solutions of pontocaine in glucose diluted to 0.05 per cent wherein ½ mg. per c.c. was injected approximately once an hour. Patients were able to lie in any position desired, and could freely move about in bed, transfer themselves to the litter and onto the delivery table without experiencing the painful cramp of uterine contractions.

The special afferent sensory autonomic pathways conveying the sensation of pain due to contraction of the upper uterine segment was shown by Cleland[4] to enter the cord through the sympathetic divisions of the 11th and 12th thoracic nerves. The pains caused by the contracting uterus before it becomes fully dilated can be completely controlled by injecting approximately ½ mg. of pontocaine per c.c. per hour. The pain caused by distention of the birth canal, and the fully dilated cervix is experienced as a severe backache, or a sharp almost constant pain in the thigh, rectum, and sometimes the lower abdomen over the region of the bladder. This type of pain reaches its zenith when the cervix is fully dilated, and is conveyed to the central nervous system partly via the sacral parasympathetics, and partly through the sacral and lumbar somatic nerves. This type of pain will not be completely relieved with the extremely dilute solution of ½ mg. or 1 c.c. per hour. It then becomes necessary to inject 1 to 1½ mg. or 2 to 3 c.c. of the dilute solution before adequate relief is obtained. By injecting these quantities at one time some but not all motor control of the extremities is lost, with only slight change in the tone of perineal musculature.

For the actual delivery the dilute solution syringe is removed and a syringe containing 4 mg. of pontocaine in glucose is substituted and injected slowly with the patient in reverse Trendelenburg position. This will completely abolish the sensation of pain, stretch, pulling, or any other discomfort caused by either spontaneous or forceps delivery, and at the same time institute profound relaxation of the perineum and birth canal. The ureteral catheter and a hyperbaric anesthetic solution make these segmental blocks both simple and possible.

Technique

The dilute anesthetic solution is mixed as follows:

Into a 20 or 30 c.c. Luer Lok syringe 1 c.c. or 10 mg. of 1 per cent pontocaine solution is aspirated. Glucose 10 per cent is then aspirated to the 20 c.c. mark. In order to prolong the action of the anesthetic ¼ c.c. of adrenalin 1:1000 is added to the solution.

The syringe is then attached to a stopcock which, in turn, is connected to a 2-inch piece of high pressure continuous spinal rubber tubing which contains a Luer connection at its opposite end (Fig. 1). This Luer connection is then locked to the 23 gauge needle which projects out of the end of the No. 3

ureteral catheter. The tubing and catheter are then washed out with several c.c. of the anesthetic solution in order to remove any autoclave debris, and is then laid aside.

A 2 c.c. Luer Lok syringe is then filled with 4 mg. or 0.4 c.c. of 1 per cent pontocaine. This is diluted to 2 c.c. with 10 per cent glucose omitting the adrenalin. A broken needle hub with solder at one end (called a nubbin) is locked onto the syringe tip in order to maintain the sterility of the contents. This is laid aside (Fig. 1).

The patient's back is then given a meticulous surgical preparation. A skin wheal is made with any suitable local anesthetic followed by ½ c.c. of methedrine or any favorite vasoconstrictor except adrenalin. The vasoconstrictor is prophylactic against a reflex fall in blood pressure which some individuals might experience only on the initial injection. Additional doses of a vasoconstrictor are unnecessary with subsequent intrathecal injections.

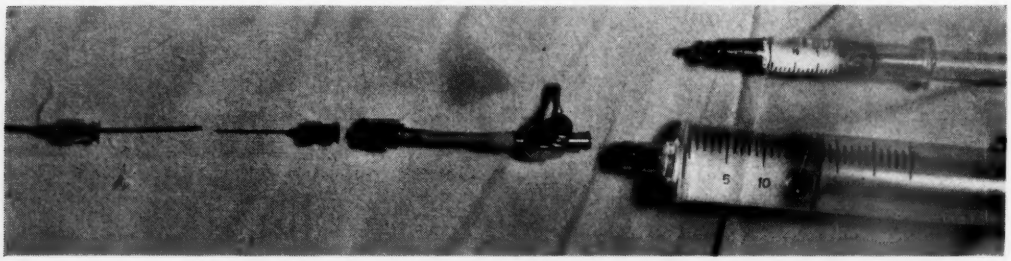

Fig. 1.—Assembly of continuous spinal equipment. The 2 c.c. syringe contains the concentrated solution with nubbin attached to tip. The 30 c.c. syringe contains the dilute solution. Stopcock attached to 2-inch piece of rubber tubing with Luer connection No. 608 L (Becton-Dickenson) at opposite end.

The 16-gauge special directional spinal needle is then inserted between the third and fourth lumbar vertebrae into the subarachnoid space. The needle is turned so that its aperture is directed cephalically, and the stilet is removed for a second, then replaced to determine whether spinal fluid is flowing freely. The catheter attached to the syringe is then picked up, the stilet again removed, and the catheter is inserted through the needle, carefully directing it cephalically into the subarachnoid space for about one inch so that its tip lies at the lower border of the second lumbar vertebra. The catheter is not inserted beyond this point so that the cord substance will at no time be contacted by the catheter. The needle is then gently withdrawn over the catheter, completely out of the back, and brought to the opposite end of the catheter (Fig. 2). *It is essential that the catheter never be pulled back through the needle once it has passed through the needle tip, since the catheter may be shorn off in the subarachnoid space by the sharp needle edge.*

The catheter is then bent over a ½-inch roll of sterile gauze and adhesived securely to the back (Fig. 2). If the gauze roll is not used the catheter tends to weaken because of the acute 90° angle made by the bend.

The patient is then asked to turn onto her back, elevating her head on a pillow (Fig. 3). The first injection consisting of 1 c.c., or ½ mg., is made, providing the cervix is not fully dilated, by exerting considerable force on the plunger. This causes the small quantity of solution to shoot up the canal past the lumbar nerves to the vicinity of the eleventh and twelfth thoracic nerves. If the solution should travel beyond this point it would become so diluted in the spinal fluid that its effect would be completely dissipated by the time it reached the fifth or sixth thoracic segments. This implies that uterine

contractions will not be impeded since the autonomic motor fibers to the uterus leave the spinal cord in this region.

The initial injection will obtund all pain due to uterine contractions, but will not paralyze the musculature innervated by the nerves with which it comes in contact. However, it will only partially obliterate the low back,

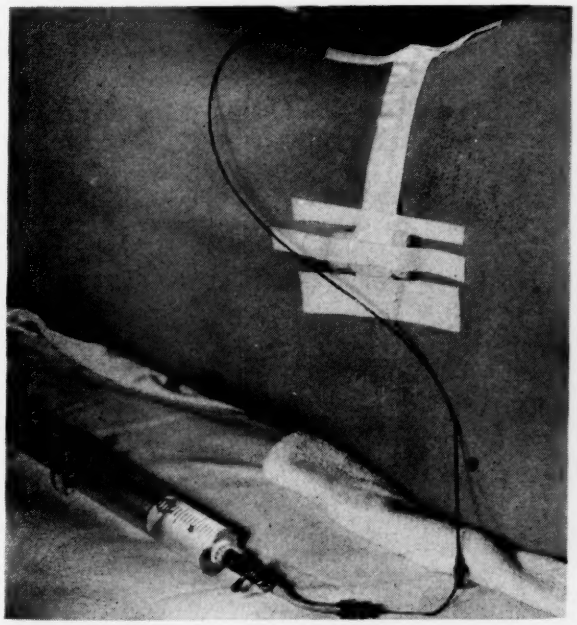

Fig. 2.—Number 3 ureteral catheter bent over roll of sterile gauze and adhesived to back. The 16 gauge needle has been withdrawn from subarachnoid space and lies at opposite end of catheter where it remains during labor and delivery.

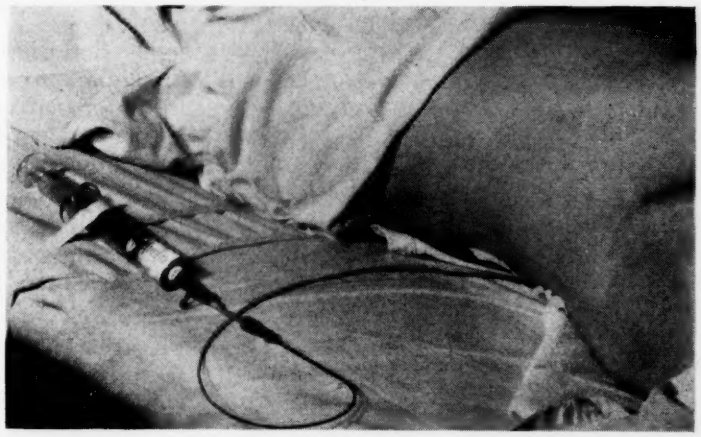

Fig. 3.—Patient well advanced in labor, lying on her back with dilute solution syringe adhesived to the bed. One c.c. or ½ mg. of pontocaine is injected approximately every hour. She has full control over all her muscles.

thigh, and rectal pain caused by progressive cervical dilatation. These latter pains are lessened somewhat, and the patient is infinitely more comfortable than before the injection.

If the initial injection is made when the cervix is fully dilated, but the head is still level with the spines, the ½ mg. or 1 c.c. dose will not be sufficient

to control the pain. It then becomes necessary to inject 2 or 3 c.c. or make a slightly more concentrated solution by adding 1 mg. of pontocaine solution to each c.c. rather than ½ mg. and injecting 1 or 2 c.c. of this. Injections to terminate the pains associated with a fully dilated cervix are made very slowly with the patient in a slight sitting position which permits the solution to fall caudally and contact the lower lumbar and sacral nerves. If "bearing down" is desired, the patient can be instructed to use her abdominal muscles synchronously with the uterine contractions since there is no muscle paralysis at this stage of the anesthetic.

When the decision is made to deliver the fetus, following a sterile vaginal examination on the delivery table in order to confirm the rectal diagnosis, the table is placed in reverse Trendelenburg position. The 2 c.c. syringe containing the 4 mg. of pontocaine in 2 c.c. of glucose is attached to the 23 gauge needle projecting from the catheter, after disconnecting the larger syringe. The solution is injected so slowly that fully two minutes should be required to inject the contents of the syringe. When the syringe is empty one minute more is allowed to elapse, after which the table may be levelled. This injection may be made while the patient is up in stirrups and completely draped. The slowness of the injection causes the hyperbaric solution to "fall" caudally in a bulk and exert its effect primarily on the sacral and lower lumbar nerves. This injection relieves all pain from vaginal, perineal, and cervical distention, and produces complete relaxation permitting episiotomy, forceps application if necessary, or any type of operative procedure required. It will produce anesthesia from one and one-half to two hours, and, because it is primarily a saddle block, the patient will be able to move her lower extremities to a certain extent.

After delivery room procedures are completed the patient is positioned as for administering the spinal and the catheter is gently and slowly removed. A sterile, antiseptic dressing is then placed over the needle area.

In general, analgesia is begun in nulliparas when the cervix is 6 to 7 cm. dilated, and in multiparas when 3 to 5 cm. dilated; the presenting part must be engaged and at least on a level with the ischial spines. If a nullipara is particularly uncomfortable before progressing to the specified dilatation, small doses of demerol or seconal are administered without scopolamine or paraldehyde since it is important to maintain a rational and cooperative patient at all times. As Hingson has stressed in his work with continuous caudal analgesia, the method was designed to relieve the pains and not the early discomforts of labor.

This type of analgesia, as with continuous caudal, is not recommended in cases of contracted pelvis, bleeding, syphilis, or tumors of the central nervous system, local infection at the site of injection, in the presence of a floating, unengaged fetal head.

Selected Case Histories

CASE 1.—A para 0-0-0-0, aged 19 years. Her antepartum course was uneventful. The initial injection of 1 c.c. or ½ mg. was given at 11:30 A.M. when the patient was 7 cm. dilated, pains every three minutes, and the head at two below the spines. At 12:20 P.M. cervix was 8 to 9 cm. dilated. She was given another ½ mg. At 1:55 P.M. the cervix was almost fully dilated and the head three below the spines, ½ mg. given. At 3:20 P.M., the patient received her final concentrated injection of 2 c.c. or 4 mg. of pontocaine in glucose while in reverse Trendelenburg position on the delivery table. The table was levelled after one minute and a central episiotomy performed. Outlet forceps were applied, and a 7-pound male delivered in left occipitoanterior position without manual or

forceps rotation at 3:32 P.M. The child cried spontaneously. Blood loss was approximately 60 c.c. There were no postpartum complications. Patient asked if she could have her next baby in the same manner.

CASE 2.—A para 2-0-0-0, aged 23 years. Her antepartum course was uneventful. The initial injection of 2 c.c. or 1 mg. was given at 9:45 P.M. when the cervix was 7 cm. dilated. Membranes were intact, and the fetal head level with the spines. At 10:35 P.M. 1 mg. was injected when the cervix was fully dilated and the head below the spines. At 11:40 P.M. another mg. was given when two below the spines. Another mg. at 12:25 A.M., and another at 1:05 A.M. At 1:35 A.M. the final concentrated injection of 4 mg. in 2 c.c. of glucose was given with the patient in reverse Trendelenburg position. At 1:45 A.M. an 8-pound male was delivered spontaneously without episiotomy and repair. The baby cried immediately. Blood loss was about 50 c.c. The postpartum course was uneventful.

Results

Contrary to the majority of reports regarding continuous caudal analgesia, we have not experienced in the present series of fifty cases any increase in operative or midforceps interference as a result of the anesthesia. In several cases where the patient was making no progress after three or more hours of analgesia, further injections were discontinued with the catheter still remaining in place, while the normal pains were permitted to return. In these cases no further progress was made, even when the patient labored and experienced unabated pain. In one case a contracted pelvis existed; in another, unsuspected twins were present. Since each injection of 1 c.c. lasts approximately forty-five minutes to one hour, it is simple to permit the parturient to resume the cognizance of her contractions by discontinuing the analgesia with the catheter still in place.

There were no maternal or fetal deaths in the series. There were no cases exhibiting a fall in blood pressure; toxic reactions of any type either to mother or child; no cases requiring supplemental anesthesia such as cyclopropane, gas, or ether; no postpartum infections at the site of needle insertion; nor were there any postpartum backaches.

There were no neurological sequelae. Postspinal headaches were not increased over what one would expect in a similar series on fifty patients undergoing general surgery under spinal anesthesia. All patients were maintained in a horizontal position for at least twelve hours post partum either on the side, back, or abdomen, depending on the patient's desire.

There were no failures to enter the subarachnoid space or to insert the ureteral catheter, and no instances of needle or catheter breakage. Catheters were used only five times and in some cases less before being discarded.

It was our impression that the first stage of labor was not retarded; the second stage remained normal but was definitely not prolonged. The patient could at all times effectively "bear down" if desired, because abdominal musculature was not paralyzed. There was no delay in the normal progress of labor whether the position of the fetus was anterior, transverse, or posterior. The third stage was of normal duration with minimal blood loss. Babies did not require resuscitation.

Complications

There were no complications of any kind in this short series. However, the possibility of complications such as meningitis, backache, shorn off catheter tip, abducens nerve palsy, persistent cephalalgia, and other neurological sequelae must always be considered.

TABLE I

PATIENT	PARITY	AT START OF ANESTHETIC: PAIN INTERVALS IN MINUTES	AT START OF ANESTHETIC: CERVIX IN CM.	AT START OF ANESTHETIC: DESCENT A—ABOVE B—BELOW L—LEVEL	AT START OF ANESTHETIC: POSITION	DELIVERY POSITION E—EPISIOTOMY S—SPONTANEOUS F—OUTLET FORCEPS FR—FORCEPS ROTATION MR—MANUAL ROTATION M—MIDFORCEPS	DURATION OF STAGES M—MINUTES H—HOURS: 1ST	2ND	3RD	DURATION OF ANESTHETIC H—HOURS M—MINUTES
36912	0000	3	7	1 B	LOA	E—F—LOA	25½ H	12 M	1 M	3 H
20717	3003	2	4	1 A	LOT	E—MR—LOT to LOA—F	12 H	2 H	3 M	6 H
24854	2000	3	7	Level	LOT	S—LOA	8½ H	2¼ H	4 M	4 H
36974	1000	3	8	2 B	LOA	F—LOA	4¼ H	45 M	5 M	45 M
36977	2002	2	10	2 B	ROA	F—ROA	10 H	30 M	2 M	45 M
36990	0000	3	7	1 B	LOT	E—M—LOA	42 H	23 M	2 M	5 H
37040	0000	3	7	2 B	ROA	E—M—ROA	15 H	50 M	11 M	6½ H
37043	0100	3	7	1 B	ROA	E—F—ROA	10 H	35 M	3 M	6½ H
37078	0000	2	10	2 B	LOT	E—MR—LOT to LOA—F	6½ H	42 M	8 M	2 H
37095	0000	3	8	1 B	LOT	E—MR—LOT to LOA—F	28 H	35 M	4 M	5 H
37113	0000	3	7	2 B	LOA	E—F—LOA	20 H	1¼ H	9 M	4 H
37102	0000	4	8	Level	ROT	E—MR—ROT to ROA—F	12 H	45 M	5 M	3 H
37044	0000	3	10	Level	LOT	E—F—LOA	17 H	2½ H	3 M	3 H
34309	2012	2	4	Level	LOT	E—F—LOA	16 H	33 M	2 M	2 H
17741	1001	3	9	2 B	LOA	S—LOA	4¼ H	2 M	6 M	45 M
37263	2002	2	5	2 B	ROA	S—ROA	2½ H	9 M	4 M	15 M
35534	0000	3	5	1 A	LOA	E—F—LOA	9 H	14 M	1 M	3 H
36588	0000	2	8	2 B		S—(Monster)	14 H	24 M	3 M	1 H
34896	0000	2	5	Level	ROT	E—FR—ROT to ROA—M	22 H	57 M	6 M	9½ H
23641	1001	3	5	1 B	LOA	S—LOA	10 H	20 M	35 M	1 H
37480	0000	2	5	Level	ROT	E—F—LOA	18 H	1¼ H	10 M	2 H
37396	0000	3	8	1 B	LOA	E—F—LOA	8 H	45 M	3 M	2 H
37513	0000	2	9	2 B	ROA	E—F—LOA	17 H	1½ H	26 M	2 H
37515	1001	2	4	1 A	LOA	E—F—LOA	20 H	45 M	1 M	3½ H
30817	1001	3	3	1 A	ROA	E—F—ROA	15 H	24 M	6 M	3 H
37531	0000	2	5	2 B	ROT	E—F—ROA	7 H	39 M	6 M	4½ H
33352	1001	3	6	1 B	ROT	E—F—ROP	7½ H	52 M	4 M	3½ H
36000	0000	2	4	2 A	ROT	E—F—ROP	19 H	40 M	30 M	10 H
33042	7007	3	3	1 A	ROA	S—ROA	21 H	7 M	5 M	2 H
36477	2001	4	5	2 B	ROA	E—F—ROA	22 H	57 M	3 M	25 M
16692	1001	3	6	1 B	LOA	S—LOA	6½ H	58 M	22 M	1½ H
36521	0000	2	9	2 B	LOA	E—F—LOA	23 H	51 M	2 M	1 H
36539	0000	3	4	1 A	LOT	E—F—LOA	19 H	2 H	20 M	5½ H
34202	2002	2	6	Level	LOA	S—LOA	13 H	11 M	4 M	56 M
36559	0000	2	9	2 B	ROA	E—F—ROA	11 H	26 M	1 M	2 H
36571	4003	2	4	2 A	LOA	S—LOA	17 H	15 M	5 M	2¼ H
36579	0000	3	6	1 B		F—LOA (Twins)	38 H	46 M	4 M	27 H
36584	0000	4	4	2 B	ROT	E—FR—ROT to ROA—M	24 H	3½ H	1 M	8½ H
36596	0000	3	5	Level	LOT	E—F—LOA	46 H	2 H	3 M	6 H
36628	0000	5	5	Level	LOT	E—MR—LOT to LOA—F	18 H	41 M	4 M	6 H
36711	0000	3	7	1 B	LOA	E—F—LOA	14 H	18 M	1 M	2 H
36758	1001	4	6	1 B	LOT	E—F—LOA	5½ H	39 M	13 M	1 H
17835	2002	3	7	2 B	ROA	S—ROA	4 H	21 M	4 M	1 H

Summary

By means of a ureteral catheter an extremely dilute solution of pontocaine in glucose is introduced into the subarachnoid space. It was demonstrated for the first time that a dilute solution of pontocaine which seems to possess no affinity for tactile, proprioceptive, thermal, pain, or motor nerves, does exert a selectivity for those nerves which convey the sensation experienced as pain from the contracting uterus without interfering with the intensity, duration, or interval of the contractions.

Since the patient retains complete skin sensation and motor tone during labor, it is necessary to substitute a more concentrated anesthetic solution just prior to the actual delivery. This is accomplished by an interchange of syringes at the distal end of the ureteral catheter, when the patient is on the delivery table and fully draped.

This approach toward the control of pain in childbirth eliminates the apprehension associated with the possibility of sudden, massive, high spinal anesthesia; hypotension due to loss of muscle tone, eliminates the necessity for constant observation of the patient, permits the patient greater freedom of movement, and removes the point of catheter insertion from the area of rectal contamination.

We feel that this new approach is a safe, practical procedure possessing many advantages over continuous caudal analgesia. Its proper niche in the field of obstetric pain relief still remains to be evaluated.

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INDUCTION OF LABOR AT THE CHICAGO LYING-IN HOSPITAL*

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IF THE termination of pregnancy is indicated after thirty-two weeks, the doctor must choose either elective cesarean section or the induction of labor. The latter would be completed preferably by vaginal delivery and rarely by cesarean section. The artificial termination of pregnancy by any method is inevitably followed by an increased fetal and maternal morbidity and mortality. In a long experience of full-time obstetrics, we have seen a number of mothers and babies die as the result of induction. The maternal deaths were due to infection or to hemorrhage and shock. The babies die from prolonged labor, infection, injuries, or from prolapsed cord. Some of these mothers and babies would undoubtedly have died from the condition under treatment which was placenta previa, abruptio placenta, or toxemia, but a number were preventable deaths.

When the Chicago maternal deaths are discussed at the monthly meetings, there is usually at least one patient in whom labor was induced for toxemia or postmaturity. The death was due to: shock and hemorrhage resulting from forcible dilatation of the cervix; infection due to long ruptured membranes; or to peritonitis resulting from cesarean section after attempts at induction of labor. In most of these cases there was no real indication for the induction, and there were at least preventable factors. The outcome could have been no worse, and in all probability, would have been much better had the induction not been carried out.

The mystery that has always interested us is not why patients go into labor after injections of solution of posterior pituitary (hereafter abbreviated to "S.O.P.P.") or mechanical induction; but why the baby has remained in utero for some forty weeks despite the well-known fact that the uterus always expels its contents (blood clots, myomas, packs, and bags). Furthermore, those patients who do not go into labor after induction are an even greater mystery. Hormone changes are not the only cause. There must be some trigger mechanism which starts the uterus into normal labor. One of us has been constantly with patients who had strong painful uterine contractions at regular intervals for as long as twenty-four hours of either spontaneous onset or due to repeated injections of S.O.P.P. However, there was no change in the amount of dilatation or in the descent of the presenting part. The uterus contracted but did not retract, which is essential for the expulsion of its contents. There was a bag of forewaters in some of these patients, but the cervix did not dilate because there was no retraction of the uterine muscle. If the

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doctor did not recognize the false labor, he would rupture membranes or insert a bag. The usual result was a long labor, a difficult delivery, uterine sepsis, and frequently a dead or injured baby. If he sent these patients home, they would come back days, or even weeks later and then have a normal labor.

Overdistention of the uterus by twins or by polyhydramnios results in premature labor, but comparable or even greater distention by a single baby whose volume may be more than that of either of the other conditions, does not result in premature labor.

The senior author during the period 1921 to 1927 had an extensive experience with induction of labor when it was used in the treatment of especially postmaturity and contracted pelves. A high fetal and maternal morbidity and mortality resulted, and we discontinued treating these conditions by induction. The staff at The Chicago Lying-in Hospital also induced labor for similar indications, but since 1933 we have been constantly decreasing the number of inductions by a better evaluation of the indication and a better selection of the optimum time. We are guided by the condition of the cervix.

During the thirty months ending June 30, 1943, there were 8,503 deliveries and 618 attempted inductions of labor, an incidence of 7.3 per cent. There were 136 failures with castor oil and quinine which are not included; 20 with S.O.P.P.; four after rupture of membranes; and one after rupture of membranes, traction on bag and S.O.P.P. One hundred eighty-three histories were deleted because although delivery occurred, the latent period after rupture of the membranes was less than one hour or longer than 12 hours after injections of S.O.P.P. Thus 276 patients, 3.2 per cent, had an induction of labor and 342 patients, 4 per cent, had a cesarean section; or a total of 616, 7.3 per cent, of our patients had the pregnancy artificially terminated. The incidence of failure was 9 per cent.

The reports[1] published since 1930 demonstrate that although there has been a decrease in the fetal and maternal mortality due to induction of labor, it is still a significant figure. The uncorrected fetal mortality ranges from 0 to 37 per cent, and the maternal from 0 to 2.8 per cent. The corrected mortality figures are much less, but still as a rule higher than the normal percentages. Browne[2] reported that 5 per cent of 173 maternal deaths in nine British maternity hospitals staffed by experts, followed directly on induction. The figures for maternal morbidity are 3 to 25 per cent. Since the average morbidity in most maternity hospitals is 7 to 10 per cent, it is obvious that the morbidity is increased with its inevitable residual damage from puerperal infection. The number of failures to initiate labor ranged from 0 to 30 per cent.

Gillett,[3] in 1944, reported a thousand consecutive inductions of labor without any failures. Labor began in all cases within twelve hours. There were no maternal deaths and no stillbirths. There were eight neonatal deaths none of which were attributable to the induction. Even though all the cases were very carefully selected, this is an unusual record.

Induction of labor is indicated in comparatively few cases as compared to twenty-five or more years ago when the cesarean section mortality was 10 per cent or more. *The primary indication must always be, is the patient better off with the uterus empty; or if the infant is alive and in good condition, is its chances of survival increased by early delivery.*

Table I lists the methods used by us for inducing labor. We have arranged the indications according to our idea of their importance.

TABLE I. INDICATIONS AND METHODS FOR INDUCTION OF LABOR

INDICATION	S.O.P.P. AND PITSULFONATE				RUPTURED MEMBRANES				R.M. AND TRACTION OR BAG AND S.O.P.P.	
			AFTER R.M.				S.O.P.P.			
	P.	M.	P.	M.	P.	M.	P.	M.	P.	M.
Placenta previa	1	1	1	1	3	7		4		4
Abruptio placenta						2				
Eclampsia					2	1		1		1
Nonconvulsive toxemia	8	8	6	1	9	9	2	4	3	1
Systemic disease		1	2	1	1	1		3		
Postmaturity	3	11			2	3	2	2		
Polyhydramnios		1		1	4	4		1		
Miscellaneous (R.M. etc.)	5	26	43	61	3	8	4	1		2
Total number	17	48	52	65	24	35	8	16	3	8=276

P = primipara; M = multipara; R.M. = ruptured membranes; S.O.P.P. = solution of posterior pituitary.

Placenta Previa.—If there is some cervical dilatation and if the previa is not a total one, we rupture the membranes. If the bleeding cannot be controlled by rupture of the membranes with traction on the head or on the foot, we perform a cesarean section. We rarely use the bag or pack.

Abruptio Placenta.—We rupture the membranes and usually these patients deliver very rapidly. During this period the patient is given adequate amounts of blood, and parenteral glucose and saline solutions. If the patient shows clinical improvement, nothing else is done. If, at the end of four to eight hours, there has been no change in the cervix and the patient on admission had presented evidence of great blood loss (indicative of complete separation and/or a Couvelaire type uterus), the case is again evaluated and a cesarean section may be performed.

Eclampsia.—After the patient has been treated medically, which requires four to six hours, a vaginal examination is made and if there is any dilatation, the membranes are ruptured. Occasionally, a bag may be introduced to hasten delivery.

Nonconvulsive Toxemia.—No one will debate but what the best treatment for toxemia is termination of the pregnancy. However, in many of the patients, the toxemia is of such a degree that the pregnancy can be permitted to continue until the baby is near term or until the cervix is ripe. Certainly, severe toxemia at any time and especially after thirty-two weeks warrants termination of the pregnancy. Our practice for many years has been to evaluate the seriousness of the toxemia and its effects on both maternal and fetal life. When the toxemic patient is two to four weeks before delivery it is amazing how much change can occur in the cervix in seven to ten days' time.

From 1931 to 1936, 21 per cent of our[4] toxemic patients were induced and 21 per cent had an abdominal delivery, a total of 42 per cent. By 1939, these figures were 14 and 9 per cent, respectively. Our fetal and maternal mortality in some 300 toxemic patients per year has been steadily decreasing primarily because of earlier recognition and treatment of the toxemia while it is still mild.

Systemic Disease.—Certain cardiac patients who have been hospitalized, are compensated and in whom the cervix is ripe, usually have labor induced by rupture of the membranes. These patients should not be permitted to carry the baby any longer than is necessary. Furthermore, induction of labor permits the optimum time to be selected. Patients with pulmonary tuberculosis, severe anemia, or diabetes mellitus, should be induced, in general, when the cervix is ripe.

Habitual Intrauterine Fetal Death.—The pregnancy is terminated at thirty-five to thirty-seven weeks by cesarean section or by induction if the cervix is ripe.

Polyhydramnios.—When the distention of the uterus causes cardiac and/or respiratory embarrassment, the membranes are ruptured. We have aspirated amniotic fluid through the abdominal wall but many of these babies are abnormal and nothing is gained by continuing the pregnancy. An x-ray should be obtained as soon as the fluid has been drained off and frequently an abnormal fetus can be detected.

Twin Pregnancy.—Because of the overdistention even though there may be 3 or more centimeters of cervical dilatation, the uterus may not contract. Rupture of the membranes, permitting as much fluid as possible to escape, will usually precipitate labor.

Convenience.—In general, induction of labor should not be carried out for the convenience of either doctor or patient. Three patients were induced for the doctors' convenience. Twelve multiparous patients who lived a considerable distance from the hospital were sent in for rupture of the membranes when the cervix was ripe. This is proper obstetrics.

Ruptured Membranes.—Patients with ruptured membranes are examined vaginally. If the cervix is ripe, they are given fractional doses of S.O.P.P., according to our routine. S.O.P.P. is not given after the membranes have been ruptured for twenty-four or more hours because of the increased likelihood of uterine rupture. If the cervix is closed, or if there is a long canal, no further measures are carried out. The patient is sent to her room, permitted to be up and about, vaginal instillations of 1 per cent merthiolate in glycerin are made every twelve hours and in from one to fourteen days most of these patients will go into labor and usually have an uneventful delivery. There is some increased risk of infection for both fetus and mother but our results for both are immeasurably better since we have discontinued the routine induction on all patients who had a spontaneous rupture of the membranes. We do not give sulfonamides and/or penicillin to these patients as a prophylaxis.

Cephalopelvic Disproportion.—We have not induced labor for many years where there was any evidence of disproportion either from a contracted pelvis or from an abnormally large baby. With cesarean section as safe as it is today the fetus should not have its life jeopardized or suffer permanent injury by induction of labor. We prefer that these patients go into labor and, if at the onset of labor there is marked disproportion, the patient must have a cesarean section. If, after a careful test of labor according to our criteria, there has been no increase in dilatation or descent of the presenting part, we perform a laparotrachelotomy.

Induction of labor for the treatment of borderline pelvic contraction has been almost given up in this country. However, a second symposium[5] on this subject in England in 1936 revealed that 40 British obstetricians were now against induction and 18 were in favor. The advocates of induction conceded a fetal mortality of 12 per cent or more although all reports stated the fetal mortality following induction for disproportion ranged from 17 to 21 per cent.

Postmaturity.—There are no criteria by which postmaturity can be determined either before or after delivery. We believe that the cervix is the best index. We do not induce labor because patients are at term or because they are overdue. Those patients in whom there is evidence of disproportion because of the size of the baby are permitted to go into labor, kept "clean" and, if necessary, a cesarean section is performed after our test of labor.

We believe it to be meddlesome obstetrics to bring patients into the hospital, attempt medical induction, and if unsuccessful, permit the patient to go home. If this can be carried out then obviously there was no need for the induction in the first place.

Cesarean section was performed in five patients who did not go into labor as a result of either S.O.P.P. and rupture of the membrane or the additional use of volsellum in two cases (cesarean-hysterectomy). There were definite indications for the operations in all cases; placenta previa in two cases and disproportion in three cases.

There were two maternal deaths, one patient had an abruptio placenta and at autopsy also had a cortical necrosis of the kidney, necrosis of the anterior lobe of the pituitary, and an eclamptic liver. Obviously the rupture of the membranes was not a factor. The other patient had been observed for some weeks and in view of the increasing severity of the toxemia it was deemed advisable to induce labor. The baby died in utero, the bag was expelled, and the uterus was ruptured by an inexperienced resident attempting to deliver an impacted shoulder in a baby weighing 1,600 grams. The death in this case was related in part to the induction.

There were 17 fetal deaths, but 4 of these weighed less than 1,500 grams. Three of the deaths were ante partum, two intra partum (one from prolapse of the cord), two from major anomalies, one from toxemia, three from previa, and two from abruptio. A corrected fetal mortality is 0.7 per cent.

Our average hospital morbidity is 9 per cent. The morbidity in patients who were induced was 14.7 per cent (38 to 38.9° C.); 4.7 per cent (39° C.+) a total of 19.4 per cent. There was only one serious case of pelvic thrombophlebitis (placenta previa). Eight patients had pyelitis, three mastitis, three respiratory infections, and one an infected episiotomy.

Table II lists the duration of the latent period and of labor for the various methods of induction. We have mentioned that many of these cases have already been deleted because the latent period was less than one hour. Since labor began within less than six hours in 65 to 91 per cent of the cases, it is obvious that the patients had been carefully selected for induction.

TABLE II. DURATION OF LATENT PERIOD AND OF LABOR

METHOD OF INDUCTION	HOURS				
	1 TO 2 (PER CENT)	2 TO 6 (PER CENT)	6 TO 12 (PER CENT)	12 TO 24 (PER CENT)	24 TO 80 (PER CENT)
S.O.P.P. or Pitsulfonate					
Primipara—Latent period	67	4		12	17
—Labor	3	28	25	25	19
Multipara—Latent period	75	9	11	5	
—Labor	26	51	15	8	
S.O.P.P. or Pitsulfonate after Spontaneous R. M.					
Primipara—Latent period	78	6	6	2	8
—Labor	3	26	43	26	2
Multipara—Latent period	81	10	3	2	4
—Labor	14	51	22	12	1
Rupture Membranes					
Primipara—Latent period	21	54	4	17	4
—Labor		35	30	22	13
Multipara—Latent period	32	34	20	12	2
—Labor	3	65	24	8	
R.M. and S.O.P.P.					
Primipara—Latent period	(50)		33	17	
—Labor		(17)	50	33	
Multipara—Latent period	26		16	42	16
—Labor		37	42	21	

( ) = less than 10 patients.

The senior obstetrician during his training had the opportunity of making frequent vaginal examinations and urges that this method of teaching be used more extensively. Certainly it is the only method which enables one to appreciate the importance of a "ripe" cervix for the successful induction of labor.

The "ripe" cervix in the primipara is one in which there is complete effacement and the cervical margins are 0.5 to 1.0 cm. thick and soft. The dilatation varies from none to 3 cm. In the multipara the canal may or may not be effaced but in either case there are 2 or more cm. dilatation and the cervix is soft. Obviously, we disagree with the authors of the various textbooks who have accepted Stieve's report. The latter stated that at term the primiparous cervical canal is 3 cm. long and that there is no dilatation. Stieve's studies are based on sections obtained at autopsy and we believe his subjects were three or more weeks from delivery although they may have been at term by menstrual date. The senior author has been periodically measuring the vaginal portion of the cervix or of the canal, if there was sufficient dilatation, for over twenty years. Studies using x-ray technique for demonstrating the length of the cervix are in progress.

Table III lists the average duration of latent period and of labor for the various methods. No conclusions are permissible because several of the groups are too small but there seems to be some indication that labor after spontaneous rupture of the membranes is longer than after artificial rupture. This is what one would expect at least in our hands because we do not rupture membranes unless the cervix is ripe. As most recent statistics indicate, the average duration of labor in both primipara and multipara is definitely less than the usual figures given in textbooks, namely eighteen and twelve hours, respectively.

TABLE III. AVERAGE DURATION OF LATENT PERIOD AND OF LABOR: HOURS

INDUCTION METHOD	PRIMIPARAS		MULTIPARAS	
	LATENT PERIOD	LABOR	LATENT PERIOD	LABOR
S.O.P.P. and Pitsulfonate	1.8	13.3	1.6	7.1
S.O.P.P. and Pitsulfonate after R.M.	1.7	11.7	1.5	9.0
Rupture Membranes	4.0	8.6	4.7	6.0
R.M. and S.O.P.P.	(3.4)	(9.2)	7.7	7.7

( ) = less than 10 cases.
R.M. = ruptured membranes.

Methods

We do not use bougie, bougie and pack, pack, stomach, or rectal tube or the intra- or extraovular injection of ether, uroselecton, hypertonic glucose or saline solution, etc. Castor oil or castor oil and quinine have also been discarded because they are of no value. If labor is to be induced with the most favorable outcome, a sterile vaginal examination must be made and the condition of the cervix determined. If it is ripe, one can be almost positive that the induction will be successful. At the time of the initial vaginal examination one must determine that there is not a forelying loop of cord or abnormal presenting part. If one contemplates a medical induction, the membranes should be stripped as high in the uterus as possible. The next morning the lower bowel is emptied by either a suppository or an enema and then either a medical induction with S.O.P.P. or rupture of the membranes is carried out. Our experience has been that induction with S.O.P.P. will fail if the cervix is

not ripe and dilated 1 or more cm. As a rule, S.O.P.P. will not produce uterine contractions at any period of pregnancy unless there is some dilatation of the cervix.

In those cases where a bag is indicated, it is used. It may be a rectal, vaginal, extra or intraovular bag. In general, we prefer to insert a bag large enough so that when it is expelled, the baby's head can follow. We attach no traction to the bag until eight to twelve hours after its insertion. We also do not use S.O.P.P. until the bag has been in place for eight to twelve hours.

Eastman[7] stated that in 85 per cent of their primiparas the head was engaged at term. This has not been our experience for many years. In about half of the primiparas, a segment of the head is through the inlet but we rarely find the head engaged even at the onset of labor. In the multipara, the head, as a rule, does not engage until the patient is well along in labor or even until after the membranes are ruptured. If the doctor is experienced, the floating head is no contraindication to rupture of the membranes providing it is done as outlined. The inexperienced doctor should not induce labor under any conditions. If uterine contractions, which need not be painful, do not begin within eight to twelve hours after rupture of the membranes, fractional doses of S.O.P.P. are given subcutaneously at 20-minute intervals.

The Drew Smythe[8] catheter which is used to rupture the membrane at the level of the baby's neck, draining off as much fluid as possible but still leaving a possible bag of forewaters, has been used extensively in various British hospitals. Labor usually begins in twenty-four hours; it may be delayed as long as three days and occasionally, as long as seven days. Some cases have required a second puncture of the membrane. There have also been deaths from sepsis after this method. We have aspirated amniotic fluid and injected solutions into the amniotic cavity through the abdominal wall to alter intrauterine pressures without being able to start labor.

Rupture of the membranes is the simplest and most effective method of starting labor. If the cervix is ripe, the duration of labor is shorter than normal. If the patients are unselected, Keettel[9] and coworkers report no increase in the average duration of labor although there is an increase in the number of prolonged parturitions.

Technique for Induction

Proper Indications and Management.—If labor is induced, there must be no sedation except nitrous oxide or ethylene until the uterine contractions are occurring every two to four minutes, lasting forty or more seconds, and cervical dilatation (vaginal examination) is increasing; when morphine and hyoscine or other sedation may be started.

Conditions.—A vaginal examination to make certain that the cervix is "ripe," that the presenting part is normal, and that there is no occult prolapse of the cord. Strip the membranes.

I. Medical: Subcutaneous injection of S.O.P.P. (obstetric) or pitocin (for toxemic patients, if available).

0 – 0.03 ml. (m ss).

20 min. – 0.06 ml. (m i) (1 international unit) if no or weak contractions.

40 min. – 0.13 ml. if no or weak contractions.

60 min. – 0.20 ml. (m iii) if no or weak contractions and *repeat* if needed until total of 1 ml. has been injected.

II. Mechanical:

a. If there is no palpable cord, strip the membranes and then rupture them, permitting as much fluid as possible to escape.
If no contractions develop within eight to twelve hours, proceed as in I or attach 200 to 500 Gm. weight to bag or forceps.

b. Bag: Vaginal, intra- or extraovular.

c. Fetal Traction:
Head—Vulsellum or Willets forceps with weight.
Leg—Fillet and weight if fetus is dead. If fetus is alive, use an adhesive skin traction.

The use of estrogen or stilbestrol for three or more days prior to the induction has been useless in a small series. If the drug or procedure used is to be given therapeutic credit, the latent period cannot be too long because eventually labor will begin in all pregnant patients.

The minute and repeated injections of S.O.P.P. used for safety are unnecessary if pitsulfonate[10] is available. The latter is a suspension of S.O.P.P. from which the active hormone is slowly liberated. The induction requires less time and there are fewer failures.

Rupture of the uterus, shock, anuria and death have been attributed to injections of S.O.P.P. One of us has seen rupture of the uterus in five patients (two died) with amounts of S.O.P.P. ranging from 0.2 to 0.3 ml.

Fatal anuria has been reported but reports by McQuarrie and co-workers[11] and our own studies indicate that even though repeated injections of S.O.P.P. are given, eventually a diuresis occurs.

S.O.P.P. produced a tetanic contraction of the uterus in five patients, 2.3 per cent. There were no uterine ruptures or fetal deaths or injuries. The uterine spasm begins to relax in five to ten minutes because of the stagnant anoxia and since it requires this long to anesthetize with chloroform and much longer with ether, it is obvious that the latter drug and probably the former also are useless for the treatment of this condition.

Pituitrin shock and/or sensitivity to pituitrin with death have been described in several reports.[12] Adelman and Lennon[13] warn against its use but in their discussion speak of "when repeated injections of pituitrin are contemplated, conservative doses should be the rule, averaging 10 to 20 pressor units for the individual dose." These are tremendous doses to use at one injection in any patients and especially in obstetric.

One of us has had a long experience at two hospitals where S.O.P.P. was used in tens of thousands of patients in judicious doses and excluding the cases of rupture of the uterus, two of which certainly could have been prevented, he has seen no patient whose life was in jeopardy from the use of S.O.P.P. There is no drug or substance that is not toxic if given in abnormally large amounts —even water is toxic under certain conditions. There is no reason why S.O.P.P. should not be used by the experienced physician. During the past year, over 1,000 patients have had 1 or 2 units of S.O.P.P. injected intravenously during the end of the second stage with no reactions.

Summary

Termination of pregnancy by induction of labor after thirty-two weeks has less indication today than it had twenty years ago. It is inevitably followed by an increased maternal and fetal morbidity and mortality irrespective of how carefully the cases are selected.

The indications for induction of labor are selected cases of placenta previa, abruptio placenta, eclampsia and nonconvulsive toxemia of pregnancy.

In the hemorrhagic groups the patients should be delivered vaginally if they possibly can be without undue hemorrhage.

In the toxemic patients one must evaluate the condition of the cervix and the severity of the toxemia. If the latter permits delay, the cervix will change and permit relatively safe induction of labor.

Induction of labor for postmaturity, contracted pelvis, convenience of patient or doctor is contraindicated.

Rupture of the membrane is the simplest and safest means of inducing labor.

Spontaneous rupture of the membranes does not necessarily imply that induction by some other means must follow.

The incidence of attempted induction of labor on our service is 3.2 per cent, and of failure is 9 per cent.

Castor oil or castor oil and quinine have no place in the induction of labor.

A vaginal examination using sterile technique should proceed all attempts at inducing labor. A careful evaluation of the pelvis, the determination of the presenting part and the exclusion of a concealed prolapse of the cord as well as the condition of the cervix must be determined. If the cervix is "ripe," labor can be successfully induced and delivery completed within twenty-four hours in over 80 per cent of the patients.

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Discussion

DR. IRVING F. STEIN.—In considering Dr. Grier's contribution, the question arises whether it is justifiable to perform induction of labor for convenience and expedience

rather than for obstetric reasons. One must first be reconciled to accept as proper the termination of pregnancy for the reasons stated, and then consider the method employed and the results.

There is no doubt that it has advantages for both patient and doctor to plan labor by appointment, but the criteria of maturity and means of accomplishment must insure the safety of both mother and her newborn babe. Dr. Grier's analysis discloses that no harm resulted from induction of labor insofar as the mothers were concerned, but the neonatal death of a baby delivered two days past the estimated due date tends to question the criteria of maturity. This child weighed five and three-fourths pounds, atelectasis being found at autopsy, suggesting prematurity. It is well known that no method of estimating full maturity of the child is entirely dependable.

A poll taken of the members of the obstetric staff at Michael Reese Hospital revealed that, although we do not routine inductions, the one method most commonly used for induction of labor is the administration of castor oil, a method abandoned by the essayist. I feel that castor oil, though objectionable to some women, is readily accepted by most obstetric patients and is a highly effective drug if given at the proper time. When given after the patient shows signs of imminent labor, after a mucous discharge or spotting, and when the cervix is completely effaced, castor oil (two ounces) usually initiates labor, no other procedure being necessary. The term "partial effacement" as employed by Dr. Grier is indefinite and is capable of a wide variance in interpretation. It is my opinion that the initiation of labor by the use of castor oil is accomplished by the removal, via the intestinal tract, of some substance which has prevented the physiologic action of the posterior pituitary gland secretion. Following the removal of this inhibitory substance, the uterus responds to the normal (posterior) pituitary stimulation, labor usually following with strong contractions and of short duration.

Success of any method of induction is assured if the cervix is fully effaced and dilated two or more centimeters. If Dr. Grier had limited himself to these criteria, his latent period would be shorter as well as the duration of labor. In estimating the latent period, had Dr. Grier figured from the time of the enema, or from the administration of calcium gluconate, instead of time of rupture of membranes, his figures would have been increased by two or more hours. They are part of his routine induction procedure.

As to the method of puncturing the membranes, I cannot subscribe to puncture with a dressing forceps guided by rectal touch alone. This I believe to be a crude and wholly unwarranted method. A comparison made some years ago at Michael Reese Hospital revealed that a single vaginal examination early in labor or before the onset of labor carried no more danger of increased morbidity than did a rectal examination. Repeated vaginal examinations definitely do increase the risk of infection. By carrying a perforator, such as our "midwife's fingernail," in the examining finger, and using it only when conditions are favorable, one need not use blunt instruments or other devices requiring a second vaginal insertion. One group at Michael Reese Hospital who induce labor electively insists that it is requisite to drain off all or most of the liquor, taking ten to twenty minutes to do so, to insure prompt uterine response to rupture of the membranes. Dr. Grier apparently obtained a satisfactory result without so doing. I would like to have him discuss this point. Does Dr. Grier claim to be able to detect forelying cord by rectal examination? How accurate is the routine diagnosis of effacement and dilatation by rectal examination alone? One is often mistaken in the rectal diagnosis.

I believe there is some justification for elective induction in selected cases, and Dr. Grier has specified conditions under which it may be carried out. Whether his method of induction is superior to others commonly employed can be best evaluated by comparison of data and results.

DR. JAMES E. FITZGERALD.—Those of you who have sat on the Maternal Welfare Committee quite well know that many patients come to the hospital with rupture of the membranes but not in labor. I also call your attention to the fact that many methods have been devised in which labor has been shortened, which includes the method of Dr.

Grier, the use of morphine in the first stage, the use of caudal anesthesia and other analgesics. I am sure that if you add them all up nothing much has happened over a period of years.

As near as I can tell in properly selected cases, there is no need to induce labor except for the convenience of the patient and the convenience of the physicians. I call your attention further to the fact that Dr. Grier quotes statistics on induction of labor. I am assuming that these inductions were done only in perfectly normal patients at or near term, not including the case of the infant that weighed five and three-fourths pounds. In these patients he has a much smaller morbidity than in the patient in whom labor is not induced; in fact, the gross fetal mortality was less than in patients who go into labor spontaneously. I am at a loss to know why stupid Nature over a period of a million years has not found that the mortality and morbidity of these patients will be decreased if she would have sense enough to rupture the membranes before the patient goes into labor.

DR. W. C. DANFORTH.—He who terminates a pregnancy before the normal onset of labor or who interferes operatively with the course of labor must be sure that he does not expose the patient to danger from which she would otherwise have been safe, and he must be certain that the procedure which he contemplates is indicated. Only in a minority of all cases of pregnancy will the initiation of labor artificially be necessary.

I agree that induction, because of cephalopelvic disproportion, should not be done, and that postmaturity alone does not warrant interference. I have on two occasions heard internists suggests that termination of labor should be done before term in cases of heart disease on the supposition that, as the baby is smaller, the labor will be easier. Any one with any real experience in obstetrics knows that this is a false hope and that induction done under such circumstances is likely to result in an unproductive labor, the woman experiencing pains perhaps for hours with no progress. An unnecessary burden is added to the already embarrassed circulation.

Dr. Dieckmann stated an important fact when he said that the cervix is the best guide. Induction, when the cervix is closed and uneffaced, is likely to require too much interference and the labor, in many cases, will be long and perhaps difficult.

I believe that packs, bougies, and the intrauterine use of chemical stimulants have no place in the obstetrics of today. Bags should be used only seldom. They may be useful in some cases of placenta previa in which delivery through the natural passage is elected and in an occasional case of toxemia in which haste is needed.

Except when termination of pregnancy is urgently indicated, induction should not be attempted when the cervix is uneffaced and closed. In cases in which such a cervix is found, and termination of pregnancy is urgently indicated, as, for example, in severe toxemia, especially in a primipara, the relative advantages of induction as compared with abdominal delivery should be carefully evaluated.

In all other cases induction should not be considered unless the conditions for easy starting of labor are present. By this is meant a cervix in which effacement is well advanced and in which some dilatation is found. The dilatation should be from one to three centimeters, and the nearer it is to the latter figure the better. In cases such as this, if the patient lives at a considerable distance from the hospital, the great haste needed to get the expectant mother to the hospital in time, and the embarrassment following a possible failure, may be avoided. Induction with these conditions present requires a minimum of trauma and morbidity is influenced but little. I agree with the statements of Dr. Dieckmann concerning the inductions formerly done which were followed by an increased fetal mortality and by maternal morbidity. I also went through a period during which we used bags in particular far more often than we do today and when we were not as selective as we are now concerning the state of the cervix. The change in our attitude toward induction has been a fortunate one.

I believe, also, that castor oil and quinine have had their day and are happily on their way to oblivion. We have found that the use of calcium, usually in the form of calcium gluconate, intravenously, followed by very small doses of pituitrin, is an effective

method and one which avoids the frequent soiling of the sterile field which occurs with castor oil and also injury to the infant which possibly may follow the use of quinine.

I do not like the stripping of the membranes. We had a considerable experience with this before the relative harmlessness of rupture of the bag, under proper conditions, became apparent. High stripping in particular requires far more invasion of the cervix and lower segment than does simple rupture, with a consequent greater likelihood of subsequent infection.

Dr. Dieckmann states that rupture of the membranes is the most effective method for the starting of labor. Rupture of the membranes may be done with any convenient instrument. We have found, especially in cases in which dilatation is two to three centimeters, and in cases in which rupture may be indicated later in labor, that the long rod-shaped perforator of Hillis, which has a sharp point at the end, may be guided by the rectal finger and the membranes ruptured. A modified dressing forceps for the same purpose has been devised by Dr. De Costa of Michael Reese. This requires a minimum of vaginal manipulation and it is recommended to those who have not used it. The low morbidity following a considerable series of inductions in our service, which has been reported this evening by Dr. Grier, I am sure, is due to the reduction of manipulation to the absolute minimum.

Induction should not be done without accurate knowledge of the pelvis and the certainty that disproportion is not present. An occult fore-lying cord should be carefully excluded. I agree fully with the statement of Dr. Dieckmann that when the cervix is "ripe" induction is nearly always successful. Induction through an undilated and uneffaced cervix may be a formidable procedure.

DR. HERBERT E. SCHMITZ.—On our service at Mercy Hospital-Loyola University Clinics we are using induction of labor where there is definite indication for the termination of pregnancy. We have considered for some time that induction for convenience is meddlesome obstetrics, although it is being carried on by one or two members of the staff but no longer with the sanction of the Department. Our opinion was based on a study carried on in 1933 to 1935 in which 200 cases were induced electively so we might evaluate the procedure. Our procedure is to send the patient to the hospital in the late afternoon, give castor oil in the morning followed by a high cleansing enema. The patient is then draped and a sterile vaginal examination is performed. We are of the opinion that only by means of a vaginal examination can we determine whether or not you have a so-called ripe cervix. No matter how much experience you have had and no matter how efficient you are in rectal examination, there is always a difference in the findings on the vaginal examination. If it is found that the cervix is ripe and there is complete effacement and at least a degree of dilatation, the membranes are then stripped as high as we can reach and then perforation of the amniotic sac is carried out. The fluid is drained as completely as possible by ballotting the head with the finger. The patient is returned to bed and if labor does not start in two hours, pituitrin is used intramuscularly in one minim doses. In this group of patients we had the same experience as to the rapidity of labor in relationship to the latent period. This I believe demonstrates conclusively our inability to recognize which cervix is ripe. The more rapid labor must mean that this procedure induces stronger contractions of the uterus, otherwise how could we account for the more rapid labor?

Feeling that this was true, I made a careful study of the postpartum period of these patients and I was surprised at the increased damage to the soft parts.

As far as commenting on Dr. Dieckmann's observation regarding priming of the cervix with estrogens before induction of labor, we have had considerable experience with this method and feel it is of no value.

DR. LUELLA E. NADELHOFFER.—Dr. Dieckmann thought it would be interesting to approach this subject from another direction, that is, from the standpoint of neonatal deaths.

An analysis was made of neonatal deaths occurring in Chicago during the year 1944. Those included the cases where there was medical or mechanical induction of labor, and termination by cesarean section, where there was no labor. The general figures showing the number of births and deaths for the year 1944 are shown in Table I.

TABLE I

	NUMBER	RATE
Live births in Chicago	59,430	20.1
Infant deaths (under 1 year)	1,789	30.1
Stillbirths	1,397	23.5
Neonatal deaths		
Under 30 days	1,250	21.0
Under 14 days	1,173	19.7
Maternal deaths	93	1.6

There were reviewed 1,145 case reports of neonatal deaths. The majority of these deaths occurring in the first few days of life; in only one case included here was the period over fourteen days. This was a tentorial hemorrhage, and the patient lived twenty-nine days.

TABLE II

Number of cases in which labor was induced		26
Medical	12	
Mechanical		
Rupture of bag of waters	13	
Bag (all placenta previa)	7	
Other means	3	
Vaginal pack		
Manual dilatation		
Self		
Termination by cesarean section		85
Low cervical	48	
Classical	33	
Porro	2	
Vaginal—1, unknown—1	2	

TABLE III

Indication for induction		26 cases
Placenta previa	9	
Toxemia (non-convulsive)	6	
Abruptio placentae	1	
Spontaneous rupture of bag of waters at term	3	
Postmaturity	4	
Uterine inertia	1	
Others: pyelitis, self	2	

TABLE IV

Indications for cesarean section			85 cases
Placenta previa		25	
Toxemia (non-convulsive)		21	
(convulsive)		3	
Abruptio placentae		10	
Previous cesarean section		14	
Disproportion		3	
Previous dead babies		3	
Medical		4	
Poliomyelitis	2		
Tuberculosis	1		
Diabetes	1		
Carcinoma of cervix		1	
Acute hydramnios		1	

The number of cases induced by medical or mechanical induction and the number terminated by cesarean section, and the types of each procedure, are shown in Table II.

In seven cases of medical or mechanical induction, a combination of two or more methods was used. In one of these, in a patient with vaginal bleeding, 1 c.c. of pituitrin was given, the bag of waters was ruptured, vaginal packing and manual dilatation were all tried.

In eight of the 12 cases of medical induction, pituitrin was used; in three cases, intranasally. One case was self-induced.

The indications for medical or mechanical induction are shown in Table III.

The indications for termination by cesarean section are shown in Table IV.

The cause of death most frequently given in the 111 cases was:

Prematurity and/or atelectasis	67
Congenital malformations	14
Intracranial hemorrhage	8
Bronchopneumonia	7
Erythroblastosis	5
Cause unknown	13

The weight of the babies was:

Under 2,500 Gm.	83
Over 2,500 Gm.	24
Unknown	7

Loss of fetal life is to be expected in a high percentage of cases where the indication for interference is hemorrhage or toxemia. One would expect where the indication for cesarean section is disproportion or repeat section, to have a living baby.

Disproportion, 3 cases:

1. 2,200 Gm.—umbilical hernia.
2. 3,634 Gm.—anencephalus and spina bifida diagnosed before operation.
3. 4,325 Gm.—hydrocephalus and spina bifida, diagnosed by x-ray before operation.

Repeat cesarean section:

3 had congenital malformations.
1 an associated placenta previa.
1 an associated toxemia.
10 weight of babies 1,360 to 2,900 Gm., atelectasis.

There were two maternal deaths:

1. A 30-year-old gravida iii, 34 weeks gestation. Toxemia, blood pressure 205/130. Classical cesarean section. Died of vaginal hemorrhage ten hours postoperatively.
2. A 37-year-old, gravida i, 28 weeks gestation. Toxemia with three convulsions. Classical cesarean section. Died from shock two hours postoperative.

The 93 cases of maternal death occurring in 1944 were also reviewed. In five cases labor was induced by mechanical means.

1. Convulsions in a 15-year-old gravida i; ruptured bag of waters.
2. Toxemia in a 275 pound patient with hypertension and 4+ albumin; 35 weeks gestation. Bag reinserted once. Died undelivered.
3. Toxemia with convulsions, 33 weeks gestation. Died undelivered.
4. Toxemia, 32 weeks gestation. Manual dilatation. Sepsis.
5. Bleeding, 33 weeks gestation. Manual dilatation. Hemorrhage.

It may be commented that, while in the majority of these cases, neonatal death was to be expected, contraindicated procedures were used in some cases and poor judgment was shown in choosing cesarean section in some cases (monstrosity) and in the time repeat section was performed in others.

In closing, there is a great deal of material for study of obstetrical practice in a review of neonatal deaths. It would also be worth while to review the cases of stillbirth occurring during labor and delivery and obstetric procedures where the mother and baby "got by."

DR. J. P. GREENHILL.—If Dr. Dieckmann is correct, that in the De Lee-Greenhill book I left in Stieve's illustration of the long cervix at term, I want to apologize. However, I am certain I did not leave it in because I do not agree with Stieve. In at least two places in the book is an entire paragraph emphasizing that regardless of a woman's calculation of the date of the last menses, if the cervix is not partly effaced and dilated the patient is not at term.

Tonight we dealt with two entirely different problems. (1) Elective induction, and (2) induction for medical and obstetric indications. Dr. Nadelhoffer's figures are not pertinent because they represent what Dr. De Lee used to call "rotten obstetrics." The two papers we heard, eminated from excellent obstetric institutions. The subject under discussion is for specialists only and not for general practitioners. I do believe that at times elective induction of labor is advisable. Every one employs a different procedure for this purpose. I strip the membranes, rupture the membranes and order an enema one hour afterwards. I rarely use pituitary extract. I never employ a bag, bougie or gauze pack. In experienced hands there are practically no dangers. The conditions which must be fulfilled are, no disproportion, a partly effaced and dilated cervix, a head presentation (although Grier reported several cases of breech presentations), and engagement of the head.

We must differentiate between elective induction in normal women and induction of labor in sick women. A certain proportion of the latter will have trouble after induction of labor.

DR. DIECKMANN (Closing).—Dr. Schmitz may be right about increased damage to the soft parts by inducing labor before the parts have been fully prepared. We have studies in progress now to determine that, but it is extremely difficult to determine the results of labor in some quantitative manner.

I disagree with Dr. Greenhill. I believe Dr. Nadelhoffer's figures are pertinent. These maternal and fetal deaths occurred during the past two years in the city of Chicago. As long as specialists try these various methods for terminating pregnancy, less experienced doctors are also going to try them with inevitable damage if not fatality. Many of the fetal and maternal deaths which occur are preventable.

I have seen quite a few expert obstetricians carry out routine induction of labor. Almost without exception each specialist has sooner or later a fetal or maternal fatality due to the induction. Having learned this during my residency, I have been extremely cautious in inducing labor in a normal patient for either the patient's convenience or mine. To date I have had no fetal or maternal mortality but I believe that there is an inevitable mortality associated with such procedures. I have had labor induced in toxemic patients and have had both fetal and maternal mortality. It has always been due to the fact that there were too many "cooks."

ELECTIVE INDUCTION OF LABOR*

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FROM Nov. 1, 1935, through Oct. 31, 1945, 10,439 women were delivered at the Evanston Hospital. Excluding bag inductions, 1,353, or 12.9 per cent, had their labors induced. In the first five of these years the incidence of induction was 10.9 per cent, and in the latter five years, 14.4 per cent. Because of this trend in our hospital, and because this procedure has been considered, by some, to be meddlesome obstetrics, it was believed that a study of our results should be made. It was our impression that our results, for both mother and child, had been good. This study has therefore been made to substantiate or disprove this impression. For one year, starting Aug. 1, 1945, a chart was kept in the labor room for recording of results when the data were fresh in the minds of all concerned. The house staff who kept these records was enthusiastic and gave constant attention to details. We therefore believe the estimate of the onset of labor may be considered accurate.

During the ten years before this study, we had made several changes in our technique for the induction of labor. We discontinued the use of castor oil, the value of which was doubtful and which was extremely unpleasant to the patient. Since the war quinine has not been available. Its absence has been beneficial, for too frequently it produced only annoying contractions, which were occasionally tetanic in character. The demonstration of deafness in the newborn following the use of quinine should outlaw this drug in obstetrics.[1] The so-called loosening or stripping of the membranes, also of dubious value, has been discontinued. In at least one case in our hands some years ago, this procedure was followed by a severe intrapartum infection which began three days after failure to start labor. We discontinued the use of obstetric pituitrin in doses as large as three minims, and now rarely use more than one minim doses. In none of the cases here reported have we observed tetanic contractions.

In the past five years a much simpler and more efficient method has developed.

Selection of Cases

We believe certain conditions should be present before the induction of labor is attempted, especially when there is no therapeutic indication. We would like to re-emphasize these important conditions, which, I am sure, are well known to all obstetricians of experience.

1. There should be no cephalopelvic disproportion.
2. The baby should be mature and should preferably present by the vertex.
3. The fetal head should be engaged or dipping well into the pelvis. It must not be floating or ballottable.

*Read before the Chicago Gynecological Society, Nov. 15, 1946.

4. The cervix should be soft, partially effaced, and dilated to at least one centimeter. These are the signs which usually precede the onset of normal labor.

In short, the onset of labor should be imminent, and obstetric prognosis good, for the elective induction of labor.

Method of Induction

When the above conditions are found upon rectal examination, the patient is informed that she may go into labor at any time. She is told that if she so desires she may select a time in the near future for her delivery. This can be made at a time most convenient for herself, her family, and her husband, to say nothing of the physician. She can make arrangements for the care of her household. In these days this is an important consideration. If she has had precipitate labors in the past, a repetition of this experience can usually be avoided by inducing labor. The patient usually enters the hospital in the morning after a night's sleep at home in her own bed. She has been instructed to have no breakfast, as anesthesia is far safer when the stomach is empty. She is admitted in a happy frame of mind without confusion. The nurse, anticipating her arrival, takes her in charge without hurry, then gives her a careful perineal preparation and a hot soapsuds enema. Soon after this the intern gives her intravenously, 10 c.c. of 10 per cent calcium gluconate solution. Usually within two hours the physician ruptures the membranes artificially. In some instances this is not necessary, as labor is so near that spontaneous rupture will follow the enema. Before the bag of waters is ruptured the perineum and vulva are cleansed with soap and water and an aqueous solution 1:2,000 zephiran chloride is poured freely over the introitus. The rupture may be done with a sterile gloved finger in the vagina to guide a perforator through the cervical opening to the membrane. We often prefer to use a dressing forceps guided rectally. We believe this does not cause as much trauma and introduces fewer bacteria than rupture done vaginally. The use of a sharp pointed perforator is more likely to leave scratches on the infant's scalp, and possibly laceration in the vagina or cervix. Before rupture is attempted the obstetrician should be certain that a forelying cord is not present. If the presenting part is fitting well into the lower uterine segment, prolapse of the cord is almost impossible. The fetal heart tones should be observed before and frequently after artificial rupture.

If labor ensues within two hours, it is allowed to progress without further stimulation. If it does not, one minim doses of pitocin are given into muscle and repeated at thirty- to sixty-minute intervals. Usually no more than two doses are required. In this series, 36 women went into labor without any need for pitocin. In none was any evidence of tetanic contractions observed.

Results

In the year from Aug. 1, 1945, through July 31, 1946, 1,284 women were delivered. There were 129 inductions, an incidence of 10 per cent. Only six of these were induced for therapeutic reasons. Four were because of severe toxemia, and two for marginal placenta previa. All the rest were considered elective inductions. There was only one which could be considered a failure. This patient was a multipara. It was thought by the physician that her membrances were ruptured artificially but they were not. This case was improperly chosen in that the head was entirely too high. She did go into labor and dilated to 7 centimeters. An x-ray revealed the infant was presenting by the face with the chin posterior. After eight and one-half hours of labor she was delivered by low cervical cesarean section.

Only five women in this series became morbid as measured by a temperature rise as high as 100.4° F. This is less than our incidence for all deliveries which is usually between 5 per cent and 6 per cent. Only one of these was febrile for four days.

There was one stillborn macerated fetus and one neonatal death. The latter was a baby two days overdue, weighing 2,620 Gm., delivered spontaneously after a labor of two hours and eighteen minutes. Autopsy disclosed only fetal atelectasis. There were two breech deliveries, several manual rotations of the head when the occiput was posterior, and our usual incidence of low forceps and spontaneous deliveries.

Thirteen women were induced eight or more days before the estimated date of term. All of these were multiparas. and all the infants survived. Thirty-five were delivered within less than a week before term. The remainder were at term or beyond.

As a rule the labors were considerably shorter than has been the rule in our service. Table I shows the time from the rupture of the membranes to the onset of labor and the duration of labor for primiparas and multiparas.

TABLE I

	RUPTURED B.O.W. TO ONSET LABOR	DURATION OF LABOR
Primiparas 34	2 hr. ± 29 min.	6 hr. 56 min. ± 44 min.
Multiparas 95	55 min. ± 5 min.	4 hr. 8 min. ± 12 min.

The most important single thing in this method of induction of labor is the rupture of the membranes. This is the time at which induction begins. The latent period is considered as the time between this rupture and the onset of labor, that is, when contractions begin. A long latent period would tend to increase intrapartum and postpartum infections. Table I shows that the average latent period for primiparas is 4 hours ± 29 minutes, and for multiparas 55 minutes ± 5 minutes. The longest latent periods for primiparas were 22 hours and 15 minutes in one, and 8 hours in another. The longest latent period for a multipara was 6 hours and 30 minutes. Even these few relatively long periods are not actually as long as one might expect. Table I also shows that the labors are as a rule much shorter than what we have come to regard as usual. In primiparas the average length of labor was 6 hours and 56 minutes ± 44 minutes, and in the multiparas it was 4 hours and 8 minutes ± 12 minutes.

Of the 34 primiparas there were thirteen whose labors were longer than the average. These are shown in Table II.

TABLE II. AVERAGE LENGTH OF LABOR IN PRIMIPARAS

6 hours 56 minutes ± 44 minutes Total 34	
More than average	13
Less than 10 hours	7
From 10 to 14 hours	3
From 14 to 24 hours	2
25 hours—10 minutes	1

Of the 95 multiparas 32 had labors longer than the average. These are shown in Table III.

Thus it is seen from Tables II and III that extremely long labors were encountered in none and relatively long labors in a very much smaller number than is usually observed.

TABLE III. AVERAGE LENGTH OF LABOR IN MULTIPARAS

4 hours 8 minutes ± 12 minutes	
Total 95	
More than average	32
Less than 8 hours	26
Less than 12 hours	3
Between 16 and 20 hours	3

It is our contention that the more completely the conditions described above are fulfilled the more smoothly will induction and labor proceed. We have compared the latent time and duration of labor in those women who have findings adequate for the induction of labor, such as slight effacement and only one centimeter dilatation of the cervix with those in whom these conditions were more advanced, namely moderate effacement to complete effacement and more than one centimeter dilatation of the cervix. There were 67 women in the former group. The time from the rupture of the membranes to the onset of labor was 1 hour 18 minutes ± 11 minutes. However in the latter group, there were 62 in whom the latent time was only 44 minutes ± 6 minutes. The duration of labor in the former group was 6 hours 18 minutes ± 39 minutes. In the latter it was 3 hours 33 minutes ± 14 minutes. Apparently the short time for the latent period and the short duration of labor verifies our contention. These results are shown in Table IV.

TABLE IV. LATENT PERIODS AND DURATION OF LABOR

	NO. CASES	RUPTURED B.O.W. TO ONSET LABOR	DURATION OF LABOR
Slight effacement and only 1 cm. dilatation	67	1 hr. 18 min. ± 11 min.	6 hr. 18 min. ± 39 min.
Moderate to complete effacement and over 1 cm. dilatation	62	44 min. ± 6 min.	3 hr. 33 min. ± 14 min.

The same may be said for another important condition, the station of the fetal head. Here two groups are shown in Table V.

TABLE V

	NO.		
Station—1 to –3 cm.	78	1 hr. 36 min. ± 14 min.	5 hr. 30 min. ± 24 min.
Station—1 or lower	51	29 min. ± 4 min.	3 hr. 34 min. ± 14 min.

In the first group are placed those in whom the station was from one centimeter above the ischial spines to three centimeters above the spines, and the second included those in whom the station was lower than one centimeter above the spines. In the former group there were 78 women in whom the latent period was 1 hour 36 minutes ± 14 minutes. In the 51 in the second group, the latent time was only 29 minutes. The duration of labor was also definitely shorter. In the first group is was 5 hours 30 minutes ± 4 minutes and in the second, 3 hours 34 minutes ± 14 minutes.

Most of these patients were given analgesia in labor. In the great majority demerol and scopolamine were administered and a much smaller number received nembutal and scopolamine. Practically all were given inhalation anesthesia by means of gas and oxygen for the termination of labor.

It was considered at the beginning of this study that an occiput posterior position of the fetal head would delay the induction time and prolong labor,

but this did not occur. There were posterior positions in 10 of the 34 primiparas and only half of these took longer than the average. Of the 95 multiparas, 31 had posterior positions and only 8 of these were longer than the average.

Discussion

Elective induction of labor has long been a subject of much controversy. Some regard it as meddlesome and vicious;[4] others state that the membranes may be ruptured with impunity.[3] We believe the procedure may be very successful in properly selected cases. We have tried in this report to show the most important conditions necessary for the selection of cases. I think we have all had failures with inductions and have been influenced by empirical laws laid down by our forebears who have condemned the procedure, rather than by a study which might show why some have failed and others have succeeded. We all have often seen long latent periods after spontaneous rupture of the membranes, when the cervix is undilated and uneffaced. In these women hours elapse before effacement takes place and dilatation begins. On the other hand, we frequently see women whose membranes rupture spontaneously, who go into labor immediately, and who sometimes deliver before they arrive at the hospital. This latter group of patients might have been spared this unfortunate experience if they had been examined more frequently rectally in the last month of pregnancy.

There are two points in which this procedure differs from other methods. Though minor, both are considered as of some importance. The first is the rupture of the membranes without introducing any part of the hand into the vagina.

The second is the use of calcium rather than castor oil and, or, quinine. Calcium has been shown clinically and experimentally, to be an effective stimulant to uterine contractility.[2] It has been suggested that an increase in the ionized calcium is requisite for the spontaneous onset of labor at term. Though the dose which is employed here is small and the effect on total circulating calcium is transient, it is believed that its administration may so alter the ratio of ionized to nonionized calcium as to increase uterine contractility. We have the distinct clinical impression that it is useful, and it is offered, therefore, as part of the method for the induction of labor here presented. The use of castor oil is not only disturbing to the patient, but it is of questionable value. The demonstration of congenital deafness following the use of quinine should eliminate this drug from obstetric use.

From this study it does not appear to us that the increase in the number of inductions at the Evanston Hospital during the past five years is cause for concern. Whereas the incidence for ten years has been 12.9 per cent, the past year in which this study was made, the incidence was 10.0 per cent. Only one induction in this series could be considered a failure. No such detailed study of this procedure has been made for the previous ten years, but it had been our impression that the results did not forbid its continued use. If still more

attention had been given to this subject, probably more women could have been selected for induction. However, it is not our ambition to induce labor in as many as possible.

Conclusions

1. The precipitation of imminent labor, by rupture of the membranes, can be very successful.

2. The proper selection of cases is most important.

3. The criteria for the proper selection of patients for induction of labor have been indicated.

4. Rupture of the membranes without the introduction of the hand into the vagina minimizes the introduction of bacteria.

5. The use of a dressing forceps, rather than a sharp pointed perforator, and its guidance through the vagina with a gloved finger in the rectum, is feasible and reduces trauma.

6. The use of quinine and castor oil is potentially harmful, often inefficient, and certainly unpleasant.

7. Calcium gluconate given intravenously has seemed to be a definite aid in producing normal and efficient uterine contractions.

8. Pituitrin in more than one minim doses is not necessary.

9. The maternal morbidity in this series is less than our general average for the past ten years.

10. The gross fetal mortality was less than 2 per cent, which is less than our general fetal mortality for these years.

11. A physician is justified in making labor easier for his patient, providing he can accomplish it safely.

12. The results here presented show that the elective induction of labor, in properly selected cases, or in other words, the precipitation of imminent labor, is a justifiable procedure.

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(For discussion, see page 504)

GONORRHEA IN GYNECOLOGY*

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GONORRHEA is still the most prevalent communicable disease in this country. Health department statistics show the incidence of the disease on the increase. In January, 1946, there were 31,305 cases of gonorrhea reported in the United States as compared with an average monthly 25,229 cases for the year 1945.[1] Interviews with outpatient gynecology clinics reveal that in most clinics "gonorrhea is not a problem." We found that few cases of gonorrhea (in the early stages before they reach the operating table for salpingo-oöpherectomy) are found in the gynecologic practice of private physicians, yet the late complications are commonly seen in the operating room. However, if smears and cultures are taken routinely the picture changes considerably. Cooke and Lankford[2] reported an incidence of 22.8 per cent of positive cultures in women attending the outpatient department of obstetrics and gynecology in Galveston, Texas. The discrepancy between the case finding of gonorrhea in male and female is great. The obvious symptoms in the male bring the patient to the physician. But why does the infected female so frequently escape the attention of the gynecologist until the patient becomes a surgical problem?

During the year March 1, 1944, to Feb. 28, 1945, 2,832 new patients were seen in the gynecologic clinic of Permanente Field Hospital, Richmond, California. This clinic served women who were employed in the Kaiser shipyards of the Richmond area, in which as many as 23,000 women were employed at one time. This clinic was not specifically known as a venereal disease clinic. Among the women seeking advice for one gynecologic complaint or another during that year 390 cases of gonorrhea were found. This means that 13.8 per cent of all new gynecologic cases were infected with gonorrhea (only bacteriologically proved cases were included in this series). This seems to be an alarmingly high percentage of venereal disease among patients in a gynecology clinic. We therefore became interested in analyzing the complaints with which these women presented themselves in order to learn what their reasons were for seeking medical help. We wanted to know whether they themselves suspected to be infected with a venereal disease and therefore came to the doctor, whether their symptoms were easily recognizable as those indicating gonorrhea, or whether their complaints seemed to be unrelated to gonorrhea. Three hundred seventeen of the 390 cases were analyzed. Table I demonstrates what we found.

*This work was carried out at the Department of Obstetrics and Gynecology, Permanente Foundation Hospitals, Oakland and Richmond, California.

TABLE I

	SINGLE COMPLAINT	TWO COMPLAINTS	THREE COMPLAINTS	FOUR COMPLAINTS	TOTAL CASES	PER CENT
Abdominal pain	79	28	7	1	115	36
Menstrual disturbances	55	15	1	1	72	23
Venereal disease?	49	1			50	16
Vaginal discharge	15	22	4		41	13
Urinary complaint	5	4	12	2	23	7
Miscellaneous	16				16	5
	219	70	24	4	317	100

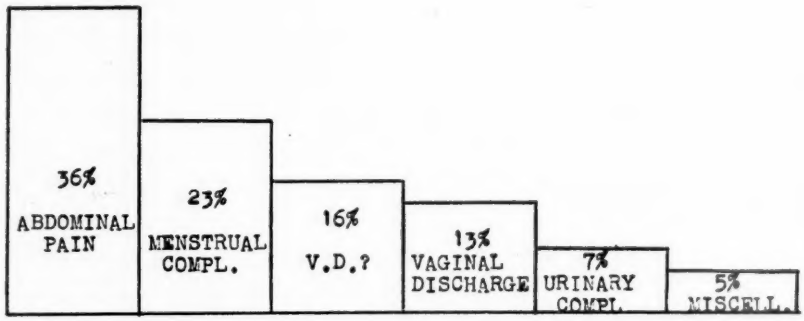

Fig. 1.—Chief complaint in 317 cases of gonorrhea in women.

Analysis of Symptoms

1. Over one-third of the women (36 per cent) found to be infected with gonorrhea came into the clinic because of abdominal pain. Of the 115 cases who presented themselves with this complaint, 79 women had abdominal pain only, while 36 had one or more complaints accompanying abdominal pain (Table I). The pain was of varying duration and location. Thirty-eight women (33 per cent) said their pain had lasted one to three days before they came to the doctor. Twenty-one (18 per cent) had had pain four to seven days before they sought help. In 28 cases (24 per cent) the pain had lasted one to four weeks. Sixteen women (14 per cent) had had pain for one month or longer before they entered the clinic. Twelve patients (11 per cent) did not know how long the pain had been present.

2. The second most frequent complaint presented was that of some menstrual irregularity. Seventy-two women entered the clinic because something had gone wrong with their menstrual period, the flow had become prolonged, menstruation had become significantly heavier than normal, or too frequent menstruation was complained about. These women did not suspect the nature of their disease, but frequently blamed the type of work they were doing for their difficulties. Stories like—"work in the shipyards does not agree with me," "sitting on cold steel makes me flow too much," often prefaced the stories of their complaint. The most frequent complaint in this group was prolonged flow. A typical story that we heard again and again was the one in which the woman stated that she had had a menstrual period of normal duration two weeks or only a few days before a new one started. This last period proved to be prolonged and unusually heavy. It was this abnormal period which usually brought the patient to seek medical help. This is such a characteristic story that we learned to put gonorrhea as our first differential diagnosis after hearing such a history. Two-thirds of the women with menstrual complaints showed the symptoms to be present for less than one month

(Table II), which only emphasizes the fact that the first abnormal period is so significantly altered that it brought the patient to the clinic.

TABLE II. MENSTRUAL DISTURBANCES

LENGTH OF TIME PRESENT	NUMBER OF CASES	PER CENT
Less than one month	48	67
One to three months	5	7
Four to six months	4	6
More than six months	1	1
Unknown	14	19
Total	72	100

But there are other menstrual disturbances that might be brought on by gonorrhea. The prolonged flow that brings the woman into the clinic after having bled for three weeks or longer might prove to be caused by the gonococcus. The menses might remain prolonged and increased in amount for weeks, even months, or might recur every eight to fourteen days. Smears and cultures taken in these cases will often reveal the real cause of their difficulties. It is commonly believed that smears and cultures taken from a bleeding cervix are of little or no value. It has been our experience that bacteriologic examination at this time will solve many problems of "functional menorrhagia," if the technique is used correctly. The technique for the collection of the bacteriologic material has been expertly described by Pelouze.[3] Material from the Skenes and Bartholins glands was collected in the usual manner. The cervix was exposed with a bivalve vaginal speculum. The cervix was then cleaned thoroughly with dry cotton applicators, and all blood and mucus wiped off. This cleaning of the cervix cannot be too much emphasized. Upon this procedure depends the success of the bacteriologist in making an accurate diagnosis. If the cervix is insufficiently cleansed the smear will be utterly confused by a multitude of organisms which may make the reading of the slide impossible, and the culture will be hopelessly overgrown by organisms. After cleaning, the cervix was then squeezed with the speculum blades to milk the cervical glands. A cotton applicator was introduced about 1 cm. into the cervical canal, and the material thus obtained spread thinly on a glass slide. Again the speculum blades were pressed together to obtain more material in the same manner for a culture. Even in a fast bleeding cervix this procedure proved to be satisfactory.

3. Fifty women (16 per cent) who proved to have gonorrhea came into the clinic wanting to know whether they had a venereal disease. They had had a suspicious contact or they just wanted a venereal disease checkup.

4. Forty-one women (13 per cent) complained about a vaginal discharge of varying duration and intensity. Some complained of and proved to have the typical creamy yellow discharge described in the textbooks as the characteristic symptom of gonorrhea. Others, however, presented as their chief complaint an itching, foamy, irritating green discharge, which is commonly seen in trichimonas vaginalis infections. Fifteen women registered vaginal discharge as their only complaint (Table I). Twenty-two women had one other symptom coupled with vaginal discharge. Abdominal pain was reported eight times in connection with the discharge. Burning, frequency, or dysuria was each coupled once with a discharge. The classical triad of vaginal discharge, frequency and burning on urination, was only reported in one case. It is worthy of note that only the fourth most frequent symptom was that of a discharge.

5. Twenty-three women (7 per cent) complained about some urinary disturbances. Frequency of urination and urgency, burning on urination, as well as bloody urine were among the complaints mentioned.

6. Sixteen women (5 per cent) had various complaints. Some were wondering whether they might be pregnant (nine cases). Three patients thought they had had a miscarriage. This fear was prompted by unusually heavy bleeding with clots and cramps. Three women complained about nausea, one of backache.

Discussion

The analysis of the complaints shows that a large percentage of cases presented symptoms which are not usually mentioned or suspected of being characteristic of gonorrhea. Almost one-fourth of the patients presented themselves with menstrual difficulties, which could have easily led to the wrong diagnosis if bacteriologic studies had not been made. In view of the fact that irregular bleeding, prolonged bleeding which at times takes on the form of hemorrhages is often the only indication of the infectious process, we must consider the possibility that some pathologic changes occur in the endometrium. Especially important seems the fact that the irregular and heavy bleeding may already appear early in the disease. If the disturbed bleeding occurs early in the ascending process it may occur in the absence of involvement of the adnexa.

A review of the literature shows that there is no unanimity of opinion as to whether the endometrium is involved in the ascending gonorrhea. Nor does the American literature mention menstrual disturbances as a frequent symptom in women with early gonorrhea, whereas the European literature stresses this symptom commonly.

Barringer,[4] discussing the symptoms of gonorrhea in the female, states "acute gonorrhea gives rise to few symptoms. There may be a little burning on urination, a slight discharge, a few colicky pains. But woman is so used to many of these symptoms. The discomfort, pain, and bladder symptoms she may consider part of a menstrual cycle." Discussing gonorrheal endometritis, Barringer says, "This condition giving rise to symptoms of menorrhagia and metrorrhagia is rare, but may be quite trying from a standpoint of diagnosis. These symptoms occur usually in young, poorly-nourished girls who have a primary virulent attack of gonorrhea. The bleeding occurs during the weeks of most active infection, and often is of such persistent type that one fears that an early malignancy may be overlooked. Presumably the bleeding is due to an acute gonorrheal endometritis with erosion which give rise to areas which bleed easily. The further probability of the uterus being in a posterior position and therefore heavy and boggy from infection adds to the mechanical element of passive congestion." Hitchman and Adler, as quoted by Te Linde,[5] insist that inflammation of the endometrium never gives rise to bleeding from the uterus. Te Linde[5] states that one frequently encounters irregularity in menstruation in acute gonorrhea, but is doubtful whether this is due to the presence of endometritis or to abnormal ovarian function dependent upon the presence of infection in the adnexa. Pelouze[6] mentions the most common early symptoms as those of the urinary tract. He states that a study of the available data upon gonococcal endometritis shows a haziness regarding the condition. He quotes Eden and Lockeyer saying

"we do not as a rule meet with acute uterine gonorrhea in gynecological practice."

If we turn to the textbooks of gynecology, the information is rather scant indeed. Symptoms of acute gonorrhea are discussed very briefly. The most frequent symptoms mentioned are those of the urinary tract and vaginal discharge. Most textbooks give long and complete discussion to chronic gonorrhea but fail to impress the reader with the variability of symptoms in acute gonorrhea and only a rare sentence is devoted to the menstrual disturbance that so frequently is found in the early stages of the disease.

Franz,[7] on the other hand, describing the symptoms of acute gonorrhea, states "characteristic for the ascending corpus gonorrhea is the increased menstruation. This is partly caused by the inflammatory hyperemia in the mucosa of the uterus and partly by mucosal defects, which are caused by inflammation. The menstruation shortly after the infection is often like a hemorrhage, at times it remains prolonged and increased in amount for months." Discussing endometritis gonorrheica "in the acute stages there is inflammatory hyperemia, swelling of the mucosa, and an increase in secretion. In the chronic stage the inflammation is mainly found in patchy distribution. Gonorrhea of the uterus is an ascending infection. First the gonococci are distributed all over the epithelium, then they penetrate the interepithelial spaces into the superficial stroma spaces. Whether the gonococci penetrate into the depth of the glands or into the muscularis is still an undecided question." Wagner,[8] in Halban and Seitz, mentions menstrual disturbances as frequent in gonorrhea. In 30 per cent of his cases the patient came to the physician only because of menstrual disturbances. He points out that the ascending gonorrheal process often follows a menstruation. This period in many cases may already be prolonged and more profuse than the previous ones. Or after a pause of only a few days profuse bleeding starts, which at times persists for several weeks with only short interruptions. Menstruation occurs too often, is prolonged and profuse. Thaler[9] found menstrual disturbances in 30 per cent of his patients with gonorrhea, Goth[10] in 31 per cent of his 700 cases. Wertheim[11] demonstrated gonococci in the endometrium eight to fourteen days (in one case already five days) after contact. Jaschke and Pankow[12] describe gonorrhea with menstrual disturbances as an outstanding symptom.

Summary

Three hundred seventeen cases of gonorrhea in women are presented. These represented 13.8 per cent of all new cases entering a gynecology clinic for varying complaints in one year.

The most frequent symptom complained about in this group was abdominal pain.

Almost one-fourth of the patients presented themselves because of menstrual disturbances. Stress is laid upon this symptom in early gonorrhea.

Bacteriologic examination of women with a history of menstrual disturbances is urged.

Conclusions

Menstrual disturbances in gonorrhea are a frequent finding. In our series it took precedence over the most widely quoted triad of symptoms of urinary frequency, urgency and vaginal discharge. In our experience it is important to make bacteriological studies on women even in the presence of bleeding. The so often quoted "higher level of suspicion" must be applied to patients in gynecological practice in order to prevent the tragedies of chronic gonorrhea which are only too familiarly seen on the operating table.

We wish to express our thanks to Martha Eaton, A.B., medical statistician, for her help in assembling the statistical material.

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CONCENTRATED PLASMA IN THE TREATMENT OF THE SEVERE LATE TOXEMIAS OF PREGNANCY

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THE use of colloidal substances to increase the osmotic pressure of the blood and effect clearing of edema and produce diuresis is not new. Dieckmann,[5] in 1931, had this principle in mind when he reported the use of 6 per cent gum acacia in severe eclamptics, with good results. His aim was to obtain a sustained blood dilution not attainable with hypertonic glucose. Dexter and Weiss suggested the trial of concentrated plasma, serum, or albumin.[6, 7]

It has been shown that there is an alteration in protein metabolism (in the liver) which begins about the third lunar month in approximately 75 per cent of apparently normal pregnancies, causing a reduction of the serum protein level. This in turn predisposes to edema.[23]

We are primarily interested in alleviating anuric and convulsive manifestations of severe toxemias of pregnancy which often terminate fatally. These findings so commonly occur together that for all practical purposes we can consider them as one, and by relieving edema and convulsions, death may be prevented. That diuresis is important will not be questioned. The most reliable sign of improvement has been diuresis, and until diuresis occurs, improvement has rarely taken place.[6]

We feel that concentrated plasma is the answer to this problem. The senior author first used concentrated plasma in 1941 in a severe eclamptic with spectacular results. Upon checking the literature at that time, little was found on the use of concentrated plasma in the late toxemias of pregnancy.

Concentrated plasma has been used in other specialties for the reduction of edema. Hughes and co-workers[13] used it to reduce intracranial pressure. They were able to reduce the cerebrospinal fluid pressure from 300 to 100 mm. of water in seventeen hours with 100 c.c. of four times concentrated plasma. Concentrated plasma has been used often to reduce the edema in nephrosis in children by Aldrich,[1] Jeans,[14] and Hill.[10] Reduction of edema has been brought about by the use of normal plasma in intestinal surgery by Ravdin and associates.[24] Beneficial results have been obtained with the use of four times concentrated plasma in edema of the upper respiratory tract.[6] Pooled serum has been used in obstetrics with excellent results by Benaran and Farnsworth[3] to stimulate diuresis in one severe eclamptic after hypertonic glucose and magnesium sulfate had failed. Hill,[12] in 1940, used 300 c.c. of four times concentrated plasma in an eclamptic in order to correct a low serum protein.

One of the most common and serious complications of the late toxemias of pregnancy is cerebral edema and/or hemorrhage. In a review by Parks[22] these conditions of the brain were a constant postmortem finding. It has been the authors' experience to find brain damage in the absence of the classically described liver of eclampsia. There seems to be little doubt that cerebral

edema as well as generalized edema are due in a large part to low serum protein levels.[22]

The administration of plasma to increase the osmotic pressure of the circulating blood is physiological. According to Best and Taylor,[4] the osmotic pressure of the plasma increases as the blood passes along the capillary, as a result of the passage of water outward and a consequent rise in concentration of protein. That is, the force holding fluid within the vessel is increased. By adding to the existing serum protein this effect will be increased, and if the plasma proteins are reduced, as they are in most severe toxemias, there will be an excess of fluid in the tissue spaces because the effective osmotic pressure is diminished.[8, 16, 18, 19, 25, 26]

In toxemias of pregnancy it has been shown that there is a diminished blood volume, hemoconcentration, and hypertension. When the filtration pressure is increased (hypertension) and is associated with a diminished colloidal osmotic pressure, the flow of urine should be increased. This is not the case in toxemias where the effective filtration pressure is not in force due to a generalized vasoconstriction which will include the afferent vessels of the glomeruli.[4] The addition of concentrated plasma will alter this condition[27] to the extent of increasing the circulating blood volume, decreasing viscosity, and rendering the blood more easily filterable by the glomeruli.

Concentrated plasma is used merely as an adjunct to the usual treatment. Hypertonic glucose solutions cannot be dispensed with.[26] These are considered to be truly diuretic in contradistinction to the action of plasma which brings about a *sustained increase* in blood volume.[11, 19] Glucose solutions are often the only source of nutrition for the comatose patient, and possibly protect the liver parenchyma against further damage as well as aid in regeneration of damage to the liver. Sedation is indicated in fulminating rises in blood pressure and nervous irritability.

We have found that less sedation is required after the administration of concentrated plasma. Concentrated plasma does not bring about a marked increase in urinary output in a patient without edema.

Concentrated plasma should not be given with impunity. Overloading of the circulatory system is easily brought about in patients with a tendency to right heart failure.[11] It has been shown that relatively large amounts of concentrated plasma given rapidly to small animals with diminished lung tissue can readily produce fatal pulmonary edema.[9] It is for this reason that we have been using only twice concentrated plasma to prevent the possibility of introducing fluid too rapidly into the circulatory system before urinary excretion and compensation by the vascular bed can take care of the added burden. If this should happen in the course of therapy, phlebotomy is advocated.[2, 11] We have not had to resort to this procedure. Reactions other than pulmonary edema have been noted. In ten thousand plasma transfusions Miller and Tisdall[17] noted 258 mild reactions which were classified as thermal and allergic. A near fatal reaction has been reported by Polayes and Squillace.[21] We have had one mild thermal reaction.

Summary

1. Concentrated plasma is a potent therapeutic agent as an adjunct in the treatment of severe late toxemias of pregnancy.

2. The colloidal osmotic action exerted by plasma is physiological. (a) It reduces edema; (b) re-establishes normal concentration of blood; (c) re-establishes circulating blood volume; and (d) increases urinary output.

3. By virtue of a decreased blood volume, toxemic patients are prone to go into vasomotor collapse following small hemorrhages. Lambeth[15] has shown that concentrated plasma will help prevent this untoward complication.

4. In the absence of edema, concentrated plasma has little effect on urinary output.

Case Reports

There has been no definite routine in handling any of the severe toxic patients at Charity Hospital. These patients were handled by three different services. The usual treatment of forcing fluids (intravenously or by mouth), sedation, careful check of urinary output, and watching for an optimal time for induction has been followed. Concentrated plasma was used upon the suggestion of the authors when all therapy had apparently failed and the patient's condition was not improving or was becoming more precarious.

Case 1.—K. B., aged 19 years, primigravida, was admitted to a home for wayward girls Sept. 19, 1941, complaining of severe headaches. Expected date of confinement was Oct. 1, 1941. Blood pressure was 190/170; the urine boiled solid. Examination: marked edema of extremities and face. Edema of eyelids was so marked they could not be opened. Treatment: morphine for nervous irritability, and hypertonic glucose infusions. The output was not recorded.

On September 20 the patient's temperature was 102° F. (ax), pulse 140, and respirations 30. Patient had one convulsion controlled by intravenous sodium amytal, followed with seconal and hypertonic glucose solutions. On examination it was found she was in labor and the presentation frank breech. Urinary output for this 24-hour period was 130 c.c. Condition was regarded as critical.

On September 21 a viable male child was delivered. Patient's condition remained unchanged. Urinary output was 60 c.c. for this 24-hour period.

On September 22 the patient's condition remained critical. In spite of hypertonic glucose therapy, the urinary output was 260 c.c. Concentrated plasma was given with almost immediate dramatic results. The following 24-hour period showed a urinary output of 3,470 c.c.

Her condition improved and the urinary output continued good. She was discharged on her fifteenth postpartal day with a normal blood pressure and no albuminuria.

Serum protein determinations were not available at this institution, and the specimen of blood was lost enroute to laboratory.

Case 2.—Mrs. J. M. H. (L-227804), aged 19 years, primigravida, was admitted Oct. 30, 1946, from prenatal clinic. Expected date of confinement was Jan. 8, 1947. During prenatal care, blood pressure was 145/100 with no albuminuria. Admission notes: marked edema of extremities and face; fundal examination revealed papilloedema with hemorrhage; blood pressure was 245/170, pulse 90, temperature 98.6° F. and respirations 25. Several hours after admission blood pressure was recorded at 190/100, and urine showed a four plus albumin with red blood cells and a few finely granular casts; serum protein 5.46, hematocrit 43, hemoglobin 14 grams, and red blood count 4,500,000. Patient was irritable. Treatment: morphine, an infusion of 1,000 c.c. of 10

per cent glucose and 500 c.c. of 20 per cent glucose were given. An indwelling catheter was inserted, and the urinary output was found to be 2,290 c.c. for twenty-four hours.

On October 31 her temperature was 101.4° F. (ax), pulse, 140, respirations 30, blood pressure 250/130. The patient had three convulsions. Luminal grains iii, $MgSO_4$ 20 c.c. of 10 per cent (i.v.), 3¾ grains sodium amytal (i.v.), 400 c.c. of 10 per cent glucose and 500 c.c. of 20 per cent glucose were given. Total output for the day was 845 c.c., and condition was regarded as poor.

On November 1 the patient's temperature was 98.6° F., pulse 90, respirations 98.6, blood pressure 200/120. Morphine and hypertonic glucose solutions were continued. Patient had no further convulsions.

Daily intravenous, hypertonic glucose and morphine were given for four days. The patient's condition remained unchanged, and the urinary output remained adequate.

On November 6 two disturbing manifestations were noted: the urinary output was reduced to 750 c.c. for twenty-four hours, and the patient had severe epistaxis. Hypertonic glucose was again given with no increase in urinary output. Concentrated plasma (300 c.c.) was given and urinary output increased to 1,600 c.c.

On November 7 the membranes were stripped in an attempt to induce labor. The output was 3,700 c.c. for this 24-hour period.

On November 8 the patient delivered a premature stillborn infant spontaneously.

On November 12 the patient deserted but had no edema. Her blood pressure was 180/100; a three plus albumin was present, and her serum proteins were 6.51.

Case 3.—Mrs. C. D. B. (T-46-214342), aged 23 years, primigravida, was admitted Nov. 19, 1946, having had no prenatal care. Expected date of confinement was Dec. 29, 1946. On admission her blood pressure was 190/130 with no demonstrable edema. Urine showed three plus albumin; serum proteins 4.7, hematocrit 45, hemoglobin 14.1 Gm., and a red blood count of 5,050,000. The patient was not in labor, so was transferred to the prenatal ward for "toxemia care." Urinary output was 1,250 c.c. for first twenty-four hours and remained adequate.

On November 22 the patient's blood pressure was 200/140, and urinary output was reduced to 650 c.c. for twenty-four hours. Fifty cubic centimeters of 50 per cent glucose and 20 c.c. of 10 per cent $MgSO_4$ were given intravenously with no improvement. Three hundred cubic centimeters of twice concentrated plasma were given with prompt increase in urinary output to 2,375 c.c. for the next twenty-four hours.

On November 23 the patient delivered, with low forceps under pudendal block, a living male infant weighing 5 pounds, 14 ounces.

Her condition steadily improved, and she was discharged on the thirteenth postpartal day, with a blood pressure of 140/100, no albuminuria, and a serum protein of 5.81.

Case 4.—Mrs. M. V. (I-45-195334), aged 20 years, Negro, primigravida, was first seen in prenatal clinic on April 17, 1946. Her prenatal course was benign except for occasional headaches. Blood pressure was within normal limits, and only on the last two visits was a one plus pedal edema noted.

On November 4 the patient was admitted with mild pains, blood pressure 138/84, two plus albuminuria, and no edema. Labor ceased shortly after admission; therefore she was transferred to prenatal ward for "toxemia care."

On November 6 the blood pressure was 160/120, blood urea nitrogen 23.5, serum protein 4.7, and hemoglobin 13 grams. Patient was sedated with luminal and given hypertonic glucose infusions.

On November 8 the albuminuria was three plus.

On November 9 the albuminuria was four plus. Patient was in labor, and urinary output dropped sharply to 200 c.c. for an eight-hour period. Three hundred cubic centimeters of twice concentrated plasma were given. The urinary output was 350 c.c. for the next two hours. This was followed by a second unit of concentrated plasma, and after an eleven-hour labor a living male infant weighing five pounds and three ounces was delivered with low forceps under local anesthesia. Urinary output was sustained to a total of 2,200 c.c. for the remainder of the day. The urinary output for three days postpartally was 3,500, 4,950, and 5,350 c.c., respectively.

On November 18 the serum proteins were 6.16.

The patient was discharged after eighteen days hospitalization, in good condition with no albuminuria, blood pressure 125/88, and no complaints.

CASE 5.—E. P. (L-46-247981), aged 18 years, Negro, primigravida, was admitted on Dec. 31, 1946, with a history of 12 to 14 major convulsions during the previous sixteen hours. She had been treated by a private physician for syphilis. For the preceding two weeks dizziness, swelling of the feet, vomiting, and severe headaches were present, and the patient consulted the doctor, who advised that the blood pressure was high. Following the convulsions, a hypodermic was given and patient sent to Charity Hospital.

On admission, the patient was drowsy but could answer questions. Blood pressure was 128/82. Examination: fetal heart tones were present, and a one plus edema of extremities. Urinalysis showed three plus albuminuria and numerous casts. Blood examinations revealed positive serology, serum proteins 4.7, hemoglobin 11.75 Gm., and a red blood count of 4,090,000. Treatment: 2,000 c.c. 10 per cent glucose and 1,000 c.c. 20 per cent glucose were given after which edema increased. Patient became comatose, and pulmonary edema developed. Blood pressure rose to 150/115, and urinary output was 650 c.c. for the night. Fifty cubic centimeters of 50 per cent glucose relieved the pulmonary edema, and the patient became responsive.

On January 1, 300 c.c. of two times concentrated plasma were given when oliguria became severe (150 c.c. in eight hours). Response was immediate and dramatic from practically no output to twenty-four drops per minute. Output was sustained for twenty-four hours at a rate of 600 to 800 c.c. per eight-hour periods.

On January 2 concentrated plasma was repeated with less dramatic results. Blood pressure rose to a maximum of 180/136. Urinary output was 300 to 500 c.c. for eight-hour periods.

On January 3 a third unit of concentrated plasma was given with a minor febrile reaction. For this reason no further plasma was given. Total twenty-four hour output was 600 c.c.

On January 5 the output was 1,775 c.c., fetal heart tones were not heard.

On January 6 the patient delivered a premature, macerated fetus. Urinary output was 2,525 c.c.

Patient steadily improved and was discharged January 22 in good condition with no edema, blood pressure 115/75, no albuminuria, and a serum protein of 5.81.

We wish to acknowledge our appreciation to Dr. Adolph Jacobs and Dr. D. W. Goldman for use of cases on their services.

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CLINICAL AND HEMATOLOGIC APLASTIC ANEMIA WITH HYPERCELLULAR MARROW IN PREGNANCY

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THE total number of cases of this type of anemia found with pregnancy is apparently very small. However, it has occurred often enough to suggest that the term "idiopathic" may no longer be fitting. Indeed, this report is being made to offer much-needed evidence that this disease may, in rare instances, be caused by pregnancy.

Several possible specific etiologic factors have been suggested, but the rare occurrence makes it likely that the actual cause will remain hypothetical for years to come. That an aplastic peripherial blood picture with pregnancy is not coincidental is reasonable but still equivocal.

Case Report

Mrs. M., a 27-year-old gravida iv para iii of Irish, French, and Indian descent, was first seen when three months pregnant. At that time she had a hemoglobin of 10 Gm. and total white cell count of 7,000. The blood was negative for syphilis and was RH positive.

First Pregnancy.—1940—As a primigravida the patient went to term without complications. There was an easy delivery of a normal baby and an uneventful postpartum course.

Second Pregnancy.—1942—Went to term without complications. Following delivery temperature went to 103° F. on one occasion, but returned to normal in thirty-six hours. Routine blood study at that time showed hemoglobin 60 per cent, red blood count 3,450,000, white blood count 5,200 with 76 per cent neutrophils, 23 per cent small lymphocytes, and 1 per cent eosinophiles.

Third Pregnancy.—1944.—Prenatal course was apparently normal until shortly before delivery. A few days before labor the patient developed diarrhea and fever. She gave a history of excessive bleeding at delivery. Routine blood study at that hospital admission revealed 6.8 Gm. hemoglobin, red blood count 2,000,000, white blood count 2,000.

Patient had a continued high fever while in the hospital and stated she "went home to die" on her fifth postpartum day with a temperature 103° F. She continued to have diarrhea, high fever, and numerous ulcers of the mouth for two months. During that time she had no medical care whatever. After two months she made a spontaneous recovery but remained weak for several weeks longer. She remained in excellent health following recovery until the onset of the present illness.

Fourth Pregnancy.—1946—With this last pregnancy the patient had a normal prenatal course until sixteen days before she delivered. At that time, Oct. 31, 1946, she came to the office complaining of several small ulcers of the mouth beneath the tongue. Local treatment was given and slight subjective improvement noticed. Five days after that office visit the patient began to bleed a little from the anus at the time of bowel movements.

The patient presented herself at the office again on Nov. 13, 1946. At this visit she was extremely pallid and weak. There was evidence of bleeding from anal fissures, and the patient stated that it had been fairly constant with an alarming total loss of blood. The ulcers of the mouth were more numerous and

larger. At that time the last blood study was Oct. 2, 1946, which showed 10.2 Gm. hemoglobin. At this visit the hemoglobin was 6 Gm. with 1,630,000 red blood cells and 2,000 white blood cells. There were 66 segmented neutrophiles, 8 stabs, and 26 lymphocytes. The patient was sent directly to the hospital for transfusion and study.

A transfusion of 500 c.c. bank blood was given the afternoon of admission, and another 1,000 c.c. given the next day. While the last transfusion was being given the patient went into labor spontaneously. It was noted that she had a heavier than normal bloody show. After a labor of approximately ten hours she delivered a normal 6 pounds, 8 ounces male baby. The placenta separated spontaneously within four minutes, and the uterus contracted nicely with very little bleeding from the uterine cavity. Episiotomy was not done. The cervix bled from several small abrasions and there was a constant oozing from a first degree laceration of the vagina. Suture and compression failed to control this bleeding after an hour's time. Vitamin K was given empirically, and finally another 500 c.c. transfusion of blood before the patient left the delivery room. Transfusion and vaginal pack apparently controlled the bleeding after about three hours.

The patient's temperature was 100° F. on admission to the hospital. It went to 101.2° F. after three hours' hospitalization and rose to 101.8° F. during labor. Within four hours after delivery the temperature was 104° F. and the patient had no complaints. From that time until the sixth postpartum day the temperature ranged between 100° and 104° F. It returned to normal the same day that the red cell count first reached 4,000,000. No evidence of infection of any type could be demonstrated during the course of high fever. There was a moderately severe diarrhea which checked when the temperature and blood picture returned to normal. The stools were negative for gross and occult blood and for ova and parasites.

Postpartum Physical Examination.—On the first postpartum day, examination revealed a very pale and weak white female who appeared older than the given age. The conjunctiva, lips, and nail beds were almost white. Ophthalmoscopic examination revealed only a pale retina—no area of hemorrhage.

There were some doubtful purpuric spots over the roof of the mouth. Several shallow grayish ulcers were seen beneath the tongue and along the lower lip and gum.

A few small submaxillary lymph nodes were palpated, but there was no generalized lymphadenopathy.

Chest examination revealed nothing more than a soft systolic murmur in the pulmonic area.

On palpation of the abdomen the liver was definitely felt one to two finger-breadths below the right costal border. The spleen could not be palpated. No other organs or masses than a first day postpartum uterus were felt.

Extremities were negative. Reflexes were bilaterally equal, and no abnormal skin sensitivity was demonstrated.

Four days after this examination multiple purpuric spots appeared over the neck, thorax, abdomen, and upper thighs. During the same period there was bleeding from the nose but with very little blood loss. The liver was not palpable after the third postpartum day.

Therapy.—Penicillin in 20,000 unit doses was given intramuscularly every three hours from the time of delivery until recovery. This was done with the thought of preventing infection during the time when the white and red cells were at such a low level.

Concentrated liver extract 2 c.c. intramuscularly daily was started on the third postpartum day. Pentnucleotide was started, but had to be discontinued after the second injection because of systemic reaction.

TABLE I

DATE	TRANSFUSION	HEMOGLOBIN (GM.)	RED BLOOD COUNT	WHITE BLOOD COUNT	SEG.	STAB	LYMPHOCYTES	MONOCYTES	EOSINOPHILES	PLATELTS	RETICULOCYTES	
1942		10.2	3,450,000	5,200	(neut.) 76	*	23		1			Delivery of second baby. Temp. 103.8° F. one reading. Normal in 36 hours
March, 1944		6.8	2,000,000	2,000								Delivery of third baby. Temperature elevation for 2 months; confined to bed for 4 months
5/30/46		11.5		7,200								Prenatal visit to office. Patient 3 months pregnant
10/ 2/46		10.2										8 months pregnant
11/13/46	500 c.c.	6.0	1,630,000	2,000	66	8	26					9 months pregnant. Admitted to hospital
11/14/46	1,000 c.c.	7.8	2,310,000									
11/15/46	500 c.c.	10.2	2,970,000	4,100	(neut.) 40		60					Delivery
11/16/46	500 c.c.											First postpartum day
11/18/46		8.5	2,670,000	600	33	18	43	1			1.6%	Third postpartum day
11/19/46	500 c.c.				(neut.) 27					None seen	0.3%	Fourth postpartum day
11/20/46	1,000 c.c.	10.5	2,920,000	1,250	(neut.) 42		58			92,000		Fifth postpartum day
11/21/46		12.9	3,760,000	1,250						26,320		Sixth postpartum day
11/22/46		11.5	4,120,000	1,500	27	20	35		3	40,000	0.6%	Seventh postpartum day
11/23/46	1,000 c.c.											Eighth postpartum day
11/25/46		14.3	4,190,000	5,400	(neut.) 62		38			167,600		Tenth postpartum day
11/27/46		14.6	4,520,000	6,750	(neut.) 76		24					Twelfth postpartum day
11/29/46		16.2	4,830,000	7,700	(neut.) 78		21		1			Fourteenth postpartum day
1/16/47		12.5	4,420,000	7,450	63	5	25	5	2	200,000		Sixty-second postpartum day
Baby's blood		18.0	5,440,000	5,150	(neut.) 32		64		4			

Blood transfusion was the chief form of therapy. Ten 500 c.c. transfusions were given, but one was discontinued before completion because of a pyrogen reaction.

TABLE II. ADDITIONAL LABORATORY DATA

	URINE	ALBUMIN FT TR, SUGAR FT TR, PUS CELLS 20-30 L.P.F., BACT. LOADED
11/16/46	Agglutination	Negative in all dilutions for typhoid "O" and "H" Paratyphoid "A" and "B" Proteus "ox 19," and B-abortus
11/18/46	Clot retraction	Not begun in 24 hours
11/18/46	X-ray	E.P.A. view of chest negative
11/18/46	Fragility test	42% beginning of hemolysis, 32% complete hemolysis
11/18/46	Icterus index	12.5 units per 100 c.c. serum
11/20/46	Serum biliruben	1.3 mg. per 100 c.c. serum
11/22/46	Feces	Occult blood negative; no ova or parasites found
11/23/46	Biopsy	Sternal bone marrow hypercellular
11/30/46	Gastric analysis	No free HCl, total acidity 9

Discussion

According to Rhoads and Miller[1] "hypercellularity of the marrow has been a particular common observation in those instances in which certain chemical substances could be identified as causative of the anemia." They cited Turnbull's findings of hypercellularity in trinitrotoluene poisoning, Anderson's in benzene poisoning and Martland's in radium poisoning.

Assuming that some by-products of pregnancy suppress the bone marrow in these cases it seems logical to expect a picture similar to that resulting from known extraneous poisons, especially when the clinical picture is of short duration.

It is regrettable that a marrow study was not made in this case when the peripherial blood showed the most severe reduction in all elements. Since the sternal biopsy was taken on Nov. 23, 1946, at which time hematologic and clinical improvement had taken place one can only guess what an earlier biopsy would have shown. However, that a marrow may change from one "very poor in cells" to one described as "cellular" in a period of four days is well proved in the case of Nieuwenhuis, cited by Hurwitt and Field.[2]

Summary

This case is significant because of the occurrence of a similar illness at about the same time in the last two pregnancies. In each case there was complete recovery following relatively prompt delivery. The recovery in the second instance was thought to be more rapid simply because the condition was recognized and treated intensively by blood transfusion.

No attempt is made to classify this as a true aplastic anemia in the strictest sense of the term. A more fitting title, as put forward by Bamford and Rhoads,[3] would be refractory anemia with hypercellular marrow.

It is felt that this case offers evidence of a causal relationship between pregnancy and an aplastic peripheral blood picture because of the above-mentioned course of the disease and the total absence of symptoms when the patient was not pregnant.

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3. Bamford, R. R., and Rhoads, C. P.: Quart J. Med. 10: 175, 1941.

CONGENITAL ANEURYSM OF THE CIRCLE OF WILLIS ASSOCIATED WITH PREGNANCY

E. E. Rhoads, M.D., Cincinnati, Ohio
(From the University Hospitals of Cleveland)

CASE 1.—W. S. was admitted to the hospital for the first time on June 22, 1932. Three days before entrance she had had a sudden attack of dizziness and fainting, and became unconscious for thirty minutes. When she regained consciousness she had a severe generalized headache and a feeling of numbness in the left side of her face, left arm, and left leg. There was no loss of function in any of these areas.

During the physical examination the patient was extremely restless and had Cheyne-Stokes' respiration. Her neck was slightly stiff. There was a questionable systolic murmur at the apex, and a blowing systolic murmur at the base. The left border of cardiac dullness was ten centimeters from the midsternal line. There was a suggestive positive Kernig test on the right side, and no Babinski reaction. The temperature was 37.5° C., pulse 66, respirations 36, and blood pressure 125/75. The cerebrospinal fluid was grossly bloody, the pressure was 550 millimeters of water, Pandy reaction was four plus, and the fluid was loaded with red blood cells; a smear of the spinal fluid sediment showed many polymorphonuclear leucocytes and many lymphocytes.

The lumbar punctures were repeated daily and on July 2, 1932, the cerebrospinal fluid showed a pressure of 190 millimeters of water and was clear. The Pandy reaction was one plus, and the cell count was only 13. The patient kept improving and was discharged July 7, 1932.

Diagnosis.—Meningeal hemorrhage.

The patient was readmitted to the University Hospitals on June 25, 1934, complaining of a severe sore throat and of a swollen, painful right knee. She gave an indefinite history of rheumatic fever at the age of 16 years.

The physical examination showed large, boggy tonsils with a moderate amount of purulent exudate. There were several small discrete nontender lymph glands in the neck. There was no abnormal precordial activity. The blood pressure was 120/70. The right knee was hot, swollen, painful on motion, and contained a large amount of fluid.

An electrocardiogram showed delayed interventricular conduction. A sedimentation rate was 2.7 millimeters per minute, and this dropped to 1.6 millimeters before discharge. The patient was given salicylates and was able to be discharged on July 4, 1934.

Diagnosis.—Acute rheumatic fever.

The patient was readmitted to the hospital on Sept. 5, 1934, complaining of chills accompanied by fever, painful respirations, and a cough. Her temperature was 40.2° C., pulse 120 and respirations 40, blood pressure 115/80. A diagnosis of lobar pneumonia was made. Antipneumococcal serum, type 1, was given, and the patient improved and was discharged on Sept. 25, 1934.

Diagnosis.—Pneumococcal lobar pneumonia, type 1, questionable acute rheumatic fever.

The patient was again admitted to the hospital on Aug. 3, 1936. She had a tonsillectomy performed. Her fifth admissian was on Sept. 18, 1939, when she had to have an appendectomy. Her condition was satisfactory following both of these operations.

After her discharge from the hospital in 1939 the patient was followed in the outpatient department. She complained at various times of headaches, palpitation, and such visual disturbances as scotoma and transient blindness. She was treated with phenobarbital.

The patient's sixth admission was on March 22, 1943, when she complained of severe headache, radiating from the occipital to the frontal region of the head. Examination showed the neck to be slightly stiff, and the pupils of the eyes were pinpoint and did not respond to light or accommodation. A lumbar puncture was done; the cerebrospinal fluid was grossly bloody, and the initial pressure of the fluid was 400 millimeters of water. Microscopic examination showed 42,000 red blood cells and 50 white blood cells per cubic millimeter; proteins were 11 per cent.*

Serial lumbar punctures were done, and on the twelfth hospital day the pressure of the spinal fluid was normal and the patient was discharged on April 10, 1943.

Diagnosis.—Subarachnoid hemorrhage due to a miliary aneurysm of the Circle of Willis.

The patient was next admitted on November 11, 1944. One week before she began to have headaches, pain in the left eye, and some swelling of the globe of this eye. The day before admission she became unconscious for three hours and, when she awoke, she had severe headache, a stiff neck, and she vomited several times.

During examination she was extremely lethargic. Her temperature was 37.4° C., pulse 72, respirations 20, and blood pressure 144/82. The pupils were contracted and there was a medium-sized round hemorrhage in the temporal portion of the left eye. The heart was slightly enlarged to the left; rhythm was normal, with a bradycardia, and a harsh systolic murmur was heard at both the apex and the base. The cerebrospinal fluid was grossly bloody; the initial pressure was over 350 millimeters of water and the final pressure was 150 millimeters.

The patient improved after lumbar punctures and on the third day the spinal fluid was nearly clear and had an initial pressure of 250 millimeters of water and a final pressure of 120 millimeters of water. She was discharged on Dec. 1, 1944.

Diagnosis.—Recurrent rupture of an aneurysm of the Circle of Willis, due to congenital arterial hypoplasia.

The patient was readmitted on Feb. 4, 1945. She was about three months pregnant, and was admitted for consideration of a therapeutic abortion. She was having occasional frontal headaches. On examination, a moderately harsh blowing systolic murmur was heard over the entire precordium which was loudest at the apex. The blood pressure was 110/70.

A consultation was held with several physicians in regard to a therapeutic abortion, and it was decided not to perform one, but that the patient should be sterilized forty-eight hours after delivery.

The patient was admitted to the obstetric service on April 4, 1945, in a semicomatose condition. With rest, she felt better, but on the morning of April 7 she had a generalized convulsion, became comatose, and had pulmonary edema. She was transferred to the medical service. Her temperature was 38.8° C., pulse 66, respirations 14, and blood pressure 210/180. The pupils reacted sluggishly to light; the left pupil was larger than the right, and there was slight papilledema bilaterally with several large hemorrhages, remote and recent. The neck was stiff and there was a constant motion of the right arm. A positive Kernig reaction was obtained. Numerous loud coarse rhonchi were heard

*As reported by laboratory.

throughout the chest. The heart was enlarged to the anterior axillary line, and there was a systolic murmur at its apex. The uterus was two fingerbreadths above the umbilicus.

The spinal fluid showed an initial pressure of over 350 millimeters and contained 2,500,000 red blood cells per cubic millimeter; proteins were 460 milligrams per cent and the platelet count was 350,000. The blood urea nitrogen was 33 milligrams per cent; serum protein 7.7 Gm.; albumin 3.8 Gm., and globulin 4.8 grams.

The patient did not regain consciousness and died of respiratory failure on April 9, 1945. An autopsy was performed and the final diagnoses were:

1. Congenital "berry" aneurysms of the Circle of Willis.
2. Bilateral bronchopneumonia with partial atelectasis of lower lobes of both lungs.
3. Hypertrophy and dilatation of the heart.
4. Gravid uterus.

CASE 2.—G. S. This patient, 27 years old, was delivered of a baby at University Hospitals on April 12, 1944. She was discharged on April 20, 1944, apparently in good condition. Her stay in the hospital was uneventful except for headaches which were on the right side and in the occipital region. On April 21, 1944, she had several generalized convulsions at home and was readmitted to the hospital.

A lumbar puncture showed clear, colorless cerebrospinal fluid, with an initial pressure of 210 millimeters of water; the microscopic examination showed 200 red blood cells and 5 white blood cells per cubic millimeter. On April 25, the patient had convulsions which began in the fingers of the right hand, spread up the right arm, involved the face, and then became generalized. She had some papilledema. She was transferred to the medical service on April 26, 1944. Her temperature was 38.8° C., pulse 70, respirations 18, and blood pressure 130/80. Examination revealed slight horizontal nystagmus, stiffness of the neck, and hyperactive reflexes. The Brudzinski sign was positive on the left side; the Gordon-Holmes sign was positive on the right side. The cerebrospinal fluid was grossly bloody and had an initial pressure of 320 millimeters of water and a final pressure of 150 millimeters of water. The Pandy test was 2 plus; red blood cell count was 12,000 per cubic millimeter, and white blood cell count was 30 per cubic millimeter, with polymorphonuclear cells predominating; proteins were 66.8 milligrams per cent. A culture of the spinal fluid showed no growth of microorganisms.

On May 5, 1944, a lumbar puncture showed an initial pressure of 350 millimeters of water and a final pressure of 110 millimeters of water, and yielded 6 cubic centimeters of xanthochromic fluid. There were 1,300 red blood cells and 5 white blood cells per cubic millimeter; proteins were 59.2 milligrams per cent.

The patient continued to have mild convulsions for two or three days with occasional nystagmus. On May 5, 1944, she developed what was thought to be a venous thrombosis of the left femoral vein. Her condition improved after rest in bed and repeated lumbar punctures and she was discharged on May 17, 1944.

Diagnoses.—Meningeal hemorrhage, probably from rupture of congenital aneurysm of the Circle of Willis. Thrombophlebitis of left femoral vein.

Comment

Congenital aneurysms of the Circle of Willis usually show few signs or symptoms until they rupture. About 50 per cent of the cases end fatally. In the series reported by Richards and Hyland, uncomplicated pregnancy was considered insignificant as a precipitating factor. However, in our first case, there are four factors that must be considered in the sequence of the five attacks of subarachnoid bleeding which resulted in the death of the patient:

1. In any pregnancy there is an increased volume strain on the vascular system.
2. The blood flow through the brain is not decreased during sleep.[5]
3. With each hemorrhage the damage done to the vessel makes it more vulnerable for subsequent bleeding.
4. Hypertension.

Hypertension is frequently present in patients with ruptured aneurysms and is probably the pre-existing condition most often found. Patients who have had vascular accidents should not have another pregnancy, because of the possibility of cardio-vascular-renal damage which is present during every pregnancy. The pressure of the fundus of the uterus on the renal vessels has been known to elevate the blood pressure.[6]

Headache is the most common symptom of intracranial hemorrhage. In patients with intracranial lesions the signs of vertigo, numbness, weakness, visual disturbances, unconsciousness, convulsions, and hemiplegia vary according to the extent and severity of the hemorrhage. Bloody spinal fluid is of utmost diagnostic importance. Many patients, without premonitory symptoms or signs, die within a short period of time.

We believe that, when a patient has had a subarachnoid hemorrhage from a ruptured congenital aneurysm or any vascular accident, contraceptive means should be used to prevent future pregnancies which are certain to be dangerous to the patient. If a cerebral hemorrhage has occurred during an early gestation period, sterilization should be carried out under local anesthesia as soon as the patient's condition permits.

Summary

1. Two cases of congenital aneurysms of the Circle of Willis associated with pregnancy have been presented.
2. The seriousness of such vascular lesions has been shown by statistical reports; the prognosis should always be guarded.
3. If a patient has a past history of hemorrhage from the rupture of an intracranial blood vessel, future pregnancies must be prevented, preferably by sterilization.
4. Pregnancy adds gravity to the prognosis because of the increased blood volume; the increased pressure of the uterus on renal vessels, and the increased strain during labor.
5. Termination of pregnancy is justified in all cases of proved bleeding from intracranial aneurysms.

I wish to thank Dr. Roscoe Leas and Dr. E. P. Kennedy for permission to report Case 2.

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Department of Reviews and Abstracts

Selected Abstracts

Gynecology

Teilum, Gunnar: Gonocytoma. Homolatous Ovarian and Testicular Tumors. I. With Discussion of "Mesonephroma Ovarii," Acta path. et microbiol. Scandinav. **23**: 242-521, 1946.

Teilum, of the University Institute of Pathological Anatomy at Copenhagen, details exhaustively the morphologic similarity between an ovarian tumor (misinterpreted, according to Teilum, by Schiller in *Am. J. Cancer*, 1939, as mesonephroma) and the more frequently encountered solid or cystic adenopapilleriferous tumors of the testis, sometimes teratoid in character. Upon a comparison between tumors of this type to seminoma (dysgerminoma) and the chorioma, the author suggests a group of two homologous tumor series between which his present case report might be considered as an "intermediate" form.

The writer feels that the gonocytomas derive their histogenetic origin from early stages of the germ cells in the testis or from the homologous remnants of the medullary cords in the ovary. In the latter organ, thus not only the dysgerminoma, but also the intermediate form (his gonocytoma II) and the primary chorioma (gonocytoma III) appear as a morphogenetically defined group originating from a particular testicular anlage. The author reports a case of ovarian mesonephroma which he is of the opinion is a true mesonephroma, in contrast to a form described erroneously by Schiller as "mesonephroma ovarii."

The writer concludes that his classification affords a foundation for a more exact histogenetic classification, comprising both ovarian and testicular tumors. C. E. FOLSOME.

Charles, A. H.: A Case of Hydatidiform Mole at Age 52, Brit. M. J. **4473**: 460, 1946.

The author reports a case of hydatidiform mole occurring in a 52-year-old gravida ii, para i. The patient, who had a Fothergill operation eight years previously, complained of two months' amenorrhea and a brown vaginal discharge of one month's duration. Carcinoma of the body of the uterus was suspected, but an endometrial biopsy revealed a mole. Treatment consisted of a total hysterectomy and bilateral salpingo-oophorectomy.

A brief review of the literature with respect to age incidence of this condition is included, and it is pointed out that hydatidiform mole occurs more frequently between the ages of 20 and 30 years, but the incidence is 2½ times greater in women over 40. Because of the possible subsequent occurrence of chorionepithelioma, he advocates total hysterectomy in women over 40 years of age. R. GORDON DOUGLAS.

O'Connor, Cornelius T., and Bradley, Joseph J.: Retroperitoneal Hemorrhage Complicating Pregnancy, New England J. Med. **235**: 648, 1946.

The authors present a report of a multipara, who, at the eighth month of gestation, developed a hematoma probably from hemorrhoidal veins, which filled the cul-de-sac of Douglas, and so caused sufficient dystocia to necessitate cesarean section. The hematoma was left undisturbed and eventually absorbed. JAMES P. MARR.

Botsford, Thomas W., and Kinney, Thomas D.: Acute Salpingitis Due to Friedländer's Bacillus, New England J. Med. **235:** 539, 1946.

The authors give a case report of an 80-year-old woman, with acute suppurative salpingitis due to Friedländer's bacillus. The bacillus was recovered from the sputum, peritoneal cavity, fallopian tube, and a postoperative wound abscess.

It is suggested that the lungs were the primary focus of infection. JAMES P. MARR.

Newborn

Wiener, A. S., and Wexler, I. B.: The Use of Heparin When Performing Exchange Blood Transfusions in Newborn Infants, J. Lab. & Clin. Med. **31:** 1016-1019, 1946.

The authors describe a simple technique they use to overcome the main obstacle to the successful performance of an exchange transfusion in infants—i.e., the problem of coagulation of infant blood upon withdrawal. This problem was circumvented by using heparin, cutting down upon several arteries, and replacing 500 c.c. via the saphenous vein. The authors admit that during "one short period the infant became pale and showed evidence of air-hunger," but concludes that their procedure might be indicated in severe cases of icterus gravis. Nine of the ten references are those of the senior author. C. E. FOLSOME.

Gruber, Seymour, Litvak, Abraham, and Jacobi, Mendel: A Case of Erythroblastosis Fetalis Caused by Isoimmunization With the Agglutinogen B, J. Pediat. **29:** 518, 1946.

A case of erythroblastosis fetalis caused by isoimmunization of an Rh-positive, type O mother by a type B baby is reported with confirmatory blood serologic findings.

It is suggested that when an erythroblastosis infant is seen, whose mother is type O and her Rh factor unknown, the baby be transfused with type O Rh-negative blood. This would obviate the possibility of giving the infant blood to which he has circulating isoagglutinins. JAMES P. MARR.

Cohen, Philip, and Scadron, Samuel J.: The Effects of Active Immunization of the Mother Upon the Offspring, J. Pediat. **29:** 609, 1946.

The authors in this well documented paper suggest an addition to prenatal care. They assert that deficiencies in immunity against diphtheria, pertussis, or any remediable infection which may be endemic may be corrected by appropriate combined immunization of the mother during pregnancy.

Apparently, as a result of childhood prophylaxis, women today lack immunity to diphtheria in about 50 per cent of cases, in contrast to 85 per cent immunity in the preimmunization era of the past generation. Also that about 80 per cent of women and about 85 per cent of babies are not immune to whooping cough as demonstrated by lack of protective antibodies. These two statements are based on sound statistical findings which the authors quote.

As an added attraction, they suggest that vaccine and toxoid therapy may serve to suppress formation of anti-Rh antibodies.

A program is presented of combined, active, maternal immunization remedying immunologic deficiencies of the mother to the immunologic advantage of the offspring. JAMES P. MARR.

Wiener, Alexander S., and Hyman, Malcolm A.: Mistreatment of Congenital Hemolytic Disease (Erythroblastosis Fetalis) by Transfusions of Rh-Positive Blood and Maternal Serum, J. Pediat. **29:** 498, 1946.

A case is presented which demonstrates the ineffectiveness of Rh-positive blood as compared with Rh-negative blood, and the danger of the use of maternal serum when treating infants with congenital hemolytic disease.

Naturally, when the infant's body contains only small amounts of Rh antibodies, the disease is self-limiting, and recovery follows whether Rh-positive or Rh-negative blood is transfused. But the argument to use Rh-positive blood when treating erythroblastosis infants in order to absorb excess antibodies and thus bring about a cure more rapidly is fallacious.

A suggestion that the mother is the ideal donor for all cases of erythroblastosis, including those due to A-B sensitization is important to remember when Rh-negative donors are not available. Two washings of her blood in saline are sufficient to remove the plasma containcy. the harmful antibody. JAMES P. MARR.

Swan, Charles, and Tostevin, A. L.: Congenital Abnormalities in Infants Following Infectious Diseases During Pregnancy, With Special References to Rubella, M. J. Australia **19:** 645, 1946.

The authors report the investigation of 56 infants and two fetuses. Forty-six of them were found to have congenital defects. In 40 instances the mothers suffered from rubella in pregnancy. Thirty-six of the infants and fetuses exhibited congenital defects. Among these cases, four of the mothers had rubella in the first month of pregnancy, 19 in the second month, eight in the third month, two in the fourth month, and one in the fifth, sixth, and eighth months. In the remaining case the duration of the pregnancy at the time of infection was not determined. In three cases in which the infant born subsequently was normal, the mothers had contracted the disease in the second, fourth, and sixth months of pregnancy, respectively. In two instances in which rubella was contracted less than a fortnight before conception, the offspring were apparently normal. The infectious diseases during pregnancy in the remaining 16 cases included eight cases of morbilli (two babies abnormal), three cases of mumps (all babies had defects), two cases of varicella (one baby deformed), two cases of herpes zoster (both babies abnormal), and one case of scarlet fever (baby defective).

WM. BERMAN.

Miller, Herbert C.: The Effect of Diabetic and Prediabetic Pregnancies on the Fetus and Newborn Infant, J. Pediat. **29:** 455, 1946.

The purpose of this paper is to review our present knowledge of diabetes and to present recent investigations that have been made on the etiology of the high fetal and neonatal mortality in diabetic pregnancies.

The tendency toward an increased birth weight among infants born to diabetic mothers is recognized by all. This has led many investigators to speculate that the growth hormone of the anterior pituitary might be not only diabetogenic for the mother, but growth producing for the fetus.

The high mortality rate of infants born of diabetic mothers has been the object of several studies carried out by White and other workers, and by Smith, Smith, and Hurwitz. The latter conclude from their investigations that there is a deficiency in the production of steroid hormones by the placenta during diabetes which causes fetal death. They have suggested large doses of diethylstilbestrol beginning about the sixteenth week of pregnancy, in order to counteract the lagging production of estrogen which apparently occurs in the latter part of some diabetic pregnancies.

White and Hunt, using estrogen and progesterone, reported marked success in lowering the number of fetal deaths.

The author is of the opinion that it is too early to judge whether or not the replacement therapy employed by the investigators mentioned is going to be uniformly successful in reducing the high mortality among offspring of diabetic mothers. JAMES P. MARR.

Pregnancy, Physiology, Etc.

Bryce, Lucy, Jakobowicz, Rachel, and McArthur, Norma: Studies of Maternal and Infantile Blood Factor Relationships, M. J. Australia **2:** 217-224, 1946.

The authors, surveying the data from Queen Victoria Hospital, the Australian Red Cross Transfusion Service, and the Walter and Eliza Hall Institute emerged with a group of

850 cases in which it was possible to examine the blood of both mother and child. They confirmed the already well-recognized importance of the Rh factor in the production of hemolytic disease of the newborn. The writers demonstrated a statistically significant effect of Rh incompatibility in relation to total fetal abnormalities, although the incidence of individual abnormalities such as stillbirth and prematurity was probably too small for valid analysis.

The authors call attention to the evidence that A, B, O incompatibility may be a cause of hemolytic disease, especially the milder manifestations such as late anemia since (1) there was a rise in the iso-agglutinin titer in the maternal serum, and (2) because in 595 cases there was complete compatibility between the maternal and infant blood in which there were only two doubtful cases of icterus gravis.

The writers report a higher incidence of icterus gravis than in most previously reported series, 10 of 850 cases, an incidence of 1 in 85 as reported; e.g., to 1 in 200 cases by Burnham. There was no correlation found between the anti-Rh titer of the maternal serum and the severity of the hemolytic disease in the infant. The iso-agglutinin titer in the maternal serum, early in pregnancy, was not significantly higher in those cases in which there was a possibility of immunization by the fetus than it was in those in which the mother and child belonged to compatible blood groups. At, or more often shortly after, delivery, the titer of the maternal isoagglutinins corresponding to the infant's A or B factor became elevated. This rise appeared to be associated in most instances with the secretor state in the infant; but in some mothers of the O group, a nonspecific rise of a much lower degree was noted in the antibody not corresponding to the infant's antigen.

Among two series of cases, the one consisting of 100 Rh-positive and 100 Rh-negative women, and the second series of 1,379 women unselected in respect to the Rh factor, there were no significant differene between the total incidence of obstetric accidents in Rh positive and Rh negative. On the other hand, there was among the Rh-negative women a significantly higher incidence of prematurity, stillbirths and *icterus gravis neonatorum*. C. E. FOLSOME.

Robbins, S. L., Parker, F., Jr., and Doyle, W. C.: The Use of the South African Frog (Xenophus Laevis) in the Diagnosis of Pregnancy, New England J. Med. 234: 784, 1946.

The extrusion of eggs by the South African clawed frog on stimulation by mammalian gonadotropic hormones, such as are excreted in the urine of women during pregnancy, offers a desirable test for pregnancy. Eight to ten hours are required for the reaction.

In a carefully controlled series of 100 consecutive routine urine analyses, the test gave no false-positive reactions, but in four cases of low-titer urines it failed to give a positive reaction. JAMES P. MARR.

Wiener, A. S., and Sonn, Eve B.: Permeability of the Human Placenta to Iso-Antibodies, J. Lab. & Clin. Med. **31:** 1020-1024, 1946.

The authors describe two cases of erythroblastosis due to A and B sensitization. By means of comparative titrations by the agglutination and conglutination techniques of the alpha and beta antibodies in the maternal and infants' sera the writers found indications that glutinins (univalent antibodies) traversed the placenta more readily than agglutinins (bivalent antibodies). The authors conclude that this evidence supports the hypothesis that glutinins, or blockers, are comprised of smaller molecules than agglutinins. Eleven of fifteen references are those of the senior author. C. E. FOLSOME.

Abortion

Bloch, Suzanne: Abortion in Mice From Injections of Colostrum and Milk, Gynaecologia **121:** 204-212, 1946.

Bloch, of the Zoological Institute at Basel University, demonstrated that the intraperitoneal injection of cow's colostrum and cow's milk produced abortion in pregnant mice.

Human colostrum, obtained before and after delivery, also caused abortion, but the human milk did not exert this effect. The toxic effect of these agents producing abortion increased with the change from cow or human colostrum to cow's milk, but was not apparent with human milk.

When progesterone was administered simultaneously it was not able to prevent the abortions produced by colostrum and milk injections. The author makes no mention of the content of fat comparison in the cow or human milk. C. E. FOLSOME.

Anesthesia, Analgesia

Brown, Arthur E.: Spinal Anesthesia and the Pregnant Woman, M. J. Australia **11**: 488, 1946.

The author reports a death from spinal anesthesia in a 29-year-old gravida vii who was to have had a cesarean section for a persistent transverse presentation. Her prenatal course had been entirely uneventful. The author reviews the literature on the susceptibility of the pregnant woman to spinal anesthesia. WILLIAM BERMAN.

Parmley, Ray T., and Adriani, John: Saddle Block Anesthesia—Its Application to Obstetrics, New Orleans M. & S. J. **99**: 373, 1947.

Experience with saddle block anesthesia in the management of labor and delivery is described. A wheal is raised with novocaine over the third lumbar interspace and an ordinary spinal needle introduced. Nupercaine, 0.5 c.c. of $\frac{1}{200}$ solution is mixed with 0.5 c.c. of 10 per cent glucose solution in a 2 c.c. syringe. This is injected into the spinal canal while the patient is in a sitting posture. The patient remains in a sitting position for thirty seconds after injection of the mixed solution. Care is taken not to inject at the height of a contraction. The hyperbaric solution being heavier than spinal fluid bathes the sacral segments and produces a sensory anesthesia over the buttocks and vulva area. Motor paralysis also occurs in the perineal muscles.

This anesthesia was used on 156 cases without serious complication. Nausea and vomiting occurred in 10 per cent. A drop in blood pressure averaging 10 mm. of mercury was observed in 50 per cent of the cases. In five cases blood pressure dropped below 80 mm. systolic, but rapidly returned to normal. Anesthesia was established within 2 to 5 minutes and lasted about three hours. WILLIAM BICKERS.

Mammary Glands

Taylor, Mary D., and Way, Stanley: Penicillin in Treatment of Acute Puerperal Mastitis, Brit. M. J. **4480**: 731, 1946.

Ten cases of puerperal mastitis are reported, only one having an abscess. This represented an incidence of one in 154 patients. Penicillin in "large" doses (12,000 to 20,000 units intramuscularly every three hours) was prescribed and nursing encouraged. Disability varied from two to seven days, but pain did not exist beyond three days. The abscess was aspirated on two occasions but was not incised. The authors emphasize the importance of early treatment and the ineffectiveness of penicillin locally. R. GORDON DOUGLAS.

Necrology

CHARLES SUMNER BACON, M.D., identified with medical progress in Chicago for more than half a century, teacher, and author, died at the Grant Hospital there on July 10, 1947, having reached almost his ninety-first year. Graduating from Northwestern University in 1884, he studied abroad for several years, and then served from 1903 to 1926 as head of the Department of Obstetrics and Gynecology at the University of Illinois. He also was associated with the former Lying-in Hospital, and for many years was active in the work of the Municipal Tuberculosis Sanitarium. Dr. Bacon was a member of many medical societies and twice president of the Chicago Gynecological Society. In 1925 he received the Golden Decoration of Honor from the Austrian Republic in recognition of his relief work after the First World War.

Correspondence

To the Editor:

Because of the prevalent opinion that the postcoital examination of the cervical mucus in the sterile patient is a fairly modern diagnostic procedure, I thought it might be of interest to call attention to the following quotation from Sims' *Uterine Surgery* (William Wood & Co., 1873, page 351).

"If we take a drop of semen from the vagina immediately after sexual intercourse, and place it under the microscope, we shall see the hurried movements of seemingly thousands of spermatozoa. But this is not the best way of studying the phenomena of their movements. The best plan is to take a drop of mucus from the canal of a perfectly normal cervix uteri some fifteen or twenty hours after sexual intercourse. We shall then be better able to examine the spermatozoa; for we shall see them in the fluid that serves as the means of their finding their way towards the ovum."

If this test is to be designated by the name of its originator therefore, probably we should call it the "Sims Test," which, I understand, is the title it is designated in England.

C. L. BUXTON, M.D.

NEW YORK, MAY 20, 1947.